The consequences of traumatic stress for the development and treatment of mental disorders: Investigating moderating factors.

Habilitationsschrift

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Hinweise zur vorliegenden Habilitationsschrift

Bei der vorliegenden Arbeit handelt es sich um eine publikationsbasierte Habilitationsschrift, welche gemäß der Habilitationsordnung des Bereichs Mathematik und Naturwissenschaften der Technischen Universität Dresden verfasst wurde. Die Arbeit ist in englischer Sprache verfasst, wobei eine Zusammenfassung in deutscher Sprache vorangestellt ist.

Die Habilitationsschrift gliedert sich in zwei Teile. Im ersten Teil werden Befunde zur Häufigkeit von psychischen Störungen nach traumatischen Ereignissen präsentiert und die Notwendigkeit der Identifikation von Moderatoren abgeleitet. Im zweiten Teil, welcher den Schwerpunkt dieser Arbeit bildet, werden verschiedene Studien zur Identifikation von möglichen Moderatoren der Folgen traumatischer Ereignisse vorgestellt. Beide Teile der Arbeit werden gesondert eingeführt und zusammenfassend diskutiert.

Die vorgelegte Habilitationsschrift basiert entsprechend der soeben beschriebenen Struktur auf den folgenden Publikationen. Die Eigenanteile an diesen Publikationen sind im Anhang kenntlich gemacht.

Teil I: The prevalence of mental disorders following traumatic event exposure

(1) **Trautmann, S.** & Wittchen, H.-U. (2018). Post-Traumatic Stress Disorder in Europe. In: Nemeroff, C. & Marmar, C. (eds.). *Post-Traumatic Stress Disorder*. New York: Oxford University Press.

(2) **Trautmann, S.**, Goodwin, L., Höfler, M., Jacobi, F., Strehle, J., Zimmermann, P., & Wittchen, H.-U. (2016). Prevalence and severity of mental disorders in military personnel: a standardised comparison with civilians. *Epidemiology and Psychiatric Sciences*, 1–10.

Teil II: Investigating moderators of adverse consequences following traumatic event exposure

(3) **Trautmann, S.**, Muehlhan, M., Kirschbaum, C., Wittchen, H.-U., Höfler, M., Stalder, T. Steudte-Schmiedgen, S. (2017). Biological stress indicators as risk markers for increased alcohol use following traumatic experiences. *Addiction Biology*. 23(1), 281-290

(4) Steudte-Schmiedgen, S., Stalder, T., Schönfeld, S., Wittchen, H.-U., **Trautmann, S.**, Alexander, N., Miller, R., Kirschbaum, C. (2015). Hair cortisol concentrations and cortisol stress reactivity predict PTSD symptom increase after trauma exposure during military deployment. *Psychoneuroendocrinology,* 59, 123-133.

(5) **Trautmann, S.**, Reineboth, M., Trikojat, K., Richter, J., Hagenaars, M., Kanske, P., Schäfer, J. (2018). Susceptibility to others' emotions moderates immediate self-reported and biological stress responses to witnessing trauma. *Behavior Research and Therapy*.

(6) **Trautmann, S**., Kräplin, A., Dietrich, R., Richter, J., Muehlhan, M. (2018). Stress-induced alcohol craving after psychological trauma: the role of childhood trauma and stress reactivity. *Psychopharmacology*.

(7) **Trautmann, S.**, Richter, J., Muehlhan, M., Hoefler, M., Wittchen, H.-U., Domschke, K., Stroehle, A., Hamm, A., Weber, H., Kircher, T., Arolt, V., Gerlach, A., Alpers, G. , Fydrich, T., Lang, T., Reif, A. (2017). Does prior traumatization affect the treatment outcome of CBT for panic disorder? The potential role of the *MAOA* gene and depression symptoms. *European Archives of Psychiatry and Clinical Neurocience*.

Deutschsprachige Zusammenfassung

Hintergrund: Traumatische Ereignisse sind definiert als Konfrontation mit tatsächlichem oder droghenden Tod, ernsthafter Verletzung oder sexueller Gewalt. Das Erleben traumatischer Ereignisse ist mit andauernder Veränderungen in biologischen und psychischen Prozesssen assoziiert, welche eine bedeutende Rolle in der Ätiologie psychischer Störungen spielen. Tatsächlich sind traumatische Ereignisse mit einem höheren Risiko für zahlreiche psychische Störungen assoziiert, darunter vor allem die Posttraumatische Belastungsstörung (PTBS) und Substanzstörungen. Zudem zeigen Personen mit traumatischen Erfahrungen häufiger ein schlechteres Ansprechen auf Behandlungen. Die Entwicklung möglichst früher Inteventionen zur Vermeidung dieser Traumafolgen ist somit von großer Bedeutung. Allerdings sind bestehende frühe Interventionen nach traumatischen Eriegnissen bislang nur sehr begrenzt effektiv. Ein wesentlicher Grund hierfür besteht darin, dass überhaupt nur ein kleiner Anteil von traumatisierten Personen negative Folgen entwickelt. Es ist demnach entscheidend, solche Faktoren zu identifizieren, die das Risiko negativer Folgen nach traumatischen Ereignissen moderieren.

Ziele: Diese Habilitationsschrift hat die folgenden Ziele: (1) Darstellung der Prävalenz von traumatischen Ereignissen und trauma-bezogenen psychischen Störungen für die Allgemeinbevölkerung und für spezifische Risikopopulationen, sowie (2) die Untersuchung von Moderatoren negativer Traumafolgen, wobei folgende potenzielle Moderatoren untersucht wurden: (i) die Ansteckbarkeit für die Emotionen anderer, (ii) Kindheitstraumata, (iii) biologische Stressmarker und (iv) ein genetischer Polymorphismus, der beim Abbau von Monoaminen involviert ist (*MAOA* Gen). Diese Moderatoren wurden in Bezug auf unterschiedliche Outcomes untersucht, welche Aspekte der Verarbeitung traumatischer Ereignisse darstellen: die

unmittelbare emotionale und biologische Reaktion, Symptome psychischer Störungen (mit Fokus auf PTBS und Alkoholkonsum) sowie das Ansprechen auf Behandlung.

Methoden: Zur Beantwortung der Fragestellungen wurden verschiedene Methoden und Studiendesigns genutzt. Diese beinhalteten zum einen epidemiologische Daten eines bundesweiten Studienprogramms bei deutschen Soldaten mit Militäreinsatz in Afghanistan. Diese Daten umfassten diagnostische Interviews sowie biologische Stressmarker. Weiterhin wurde eine experimentelle randomisierte Analogstudie durchgeführt, um Moderatoren von initialen Traumareaktionen zu identifizieren. Schließlich wurden Daten einer Multi-Center Therapiestudie bei Patienten mit Paniskstörung und Agoraphobie verwendet, um die Moderation des Effekts vorangegangener Traumatisierung auf den Therapieerfolg durch einen genetischen Faktor (*MAOA* Gen) zu untersuchen.

Hauptergebnisse: Nur ein geringer Anteil von Betroffenen entwickelt nach der Konfrontation mit einem trauamtischen Ereignis psychische Störungen. Dies gilt auch in Populationen mit einem erhöhten Risiko für multiple und schwere Traumata. Die durchgeführten Studien zur Identifikation von Moderatoren weisen darauf hin, dass Personen mit einer erhöhten Ansteckbarkeit für negative Emotionen anderer eine stärkere initiale Stressreaktion bei Traumaexposition aufweisen. Darüber hinaus zeigen Männer mit Traumatisierung in der Kindheit einen stärkeren Anstieg von Alkoholcraving nach der Konfrontation mit einem akuten Trauma. Weiterhin sind niedrige basale Cortisol Level mit einem höheren Risiko für einen Anstieg der PTBS Symptomatik sowie im Alkoholkonsum nach traumatischen Ereignissen assoziiert. Schließlich gibt es Hinweise auf geringere Therapieeffekte bei vorangegangener Traumatisierung bei einer Subgruppe von weiblichen Patientinnen mit Panikstörung mit der niedrig aktiven Variante des *MAOA* Gens.

Schlussfolgerungen: Es konnten neue Kandidaten für mögliche Moderatoren identifiziert sowie die Relevanz bekannter Moderatoren in neuen Kontexten gezeigt werden. Einige dieser

Moderatorvariablen stellen vielversprechende Ziele für Risikomarker vor und unmittelbar nach der Konfrontation mir traumatischen Ereignissen dar. Weitere Forschung ist nötig, um die hier identifizierten Moderatoren zu bestätigen und die zugrundeliegenden Mechanismen aufzudecken. Zudem sollte künftige Forschung die Befunde zu verschiedenen Moderatoren integrieren um daraus effektive Risikobewertungen und gezielte Frühinterventionen ableiten zu können.

Content

Executive summary

Background: Per definition, traumatic events include exposures to death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence. Exposure to traumatic events is associated with persistent alterations in biological and psychological processes that are involved in the etiology of mental disorders. In fact, traumatic events are associated with a higher risk for various mental disorders such as posttraumatic stress disorder (PTSD) and substance use disorders, but also with treatment resistance. Thus, it is crucial to develop early interventions to prevent these adverse trauma-related outcomes. However, existing pharmacological and psychological early intervenions only have a limited efficacy so far. A major reason is that only a minority of trauma-exposed individuals actually develops adverse consequences making universally applied interventions ineffective. Thus, it is crucial to identify moderators of adverse responses to trauma exposure.

Aims: This thesis aimed at (1) providing estimates on the prevelance of traumatic event exposure and trauma-related mental disorders for the general population and high-risk populations and (2) investigating moderators of adverse mental health consequences following traumatic event exposure. The following potential moderators were investigated: (i) the susceptibility to others' emotions, (ii) childhood traumas, (iii) biological stress markers and (iv) a specific genetic polymorphism involved in the degradation of monoamines (i.e. *MAOA* gene). These investigations were conducted with respect to differenct outcomes relevant in the processing of traumatic events including the initial affective and biological reaction, mental disorder symptoms (focusing on PTSD and alcohol use symptoms) and treatment response.

Methods: To answer the research questions, different methods and designs were applied. First, epidemiological data from a national study program in German soldiers deployed to Afghanistan were used. These data included diagnostic interview data as well as biological markers. Second, an experimental study with a randomized trauma analogue design was used to investigate

moderators of acute trauma responses. Third, a genetic moderator of trauma effects on treatment response was investigated using data from a multi-center trial of exposure-based cognitive behavioral therapy of panic and agoraphobia patients.

Main results: Only a small minority of trauma-exposed individuals develops mental disorders. This also applies to populations with a high risk for multiple and/or severe trauma exposure. The investigations of potential moderators suggeted that individuals with a higher susceptibility to negative emotions of others show a higher stress reactivity after trauma exposure. Males with childhood traumas show a higher increase in alcohol craving after trauma exposure. Moreover, individuals with lower basal cortisol levels have a higher risk of increased PTSD symptoms and alcohol use following trauma exposure. Finally, a subgroup of traumatized female panic disorder patients with the low-active variant of the *MAOA* gene benefits less from exposure-based psychotherapy.

Conclusions: These findings suggest novel targets for moderating factors and show the relevance of previously discovered moderators in novel contexts. Some of the identified moderators represent promising targets for risk markers before or in the direct aftermath of traumatic event exposure. Further research is needed to comfirm the suggested moderators and to investigate the exact mechanisms involved. Moreover, future studies should aim at integrating findings on different moderators and translate them into effective risk assessments and targeted early interventions.

1 Introduction

1.1 Definition traumatic event

The exposure to stress in various forms is a major component in theories and models trying to explain the etiology of mental disorders in clinical psychology. Stress exposure can be defined as condition in which expectations, whether genetically programmed, established by prior learning, or deduced from circumstances, do not match the current or anticipated perceptions of the internal or external environment, and this discrepancy between what is observed or sensed and what is expected or programmed elicits patterned, compensatory responses (Goldstein, 1990). While mild to moderate stressful experiences, which are within the capabilities of an individual to overcome, can produce a sense of mastery and accomplishment that eventually result in a positive outcome, adverse experiences that exceed the coping abilities of the individual can increase the risk for mental disorders (Levine, 2005; McEwen, 2000; Sinha, 2008). The most severe forms of stressful experiences are extreme adversities that threaten the life, physical integrity and health of oneself and one's loved ones (Keyes, Hatzenbuehler, & Hasin, 2011). Such experiences have been labelled traumatic.

In the latest edition of the Diagnostic and Statistical Manual of Mental Disorder (DSM-5, APA, 2013), traumatic events are defined as:

> *"Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:*
>
> *1. directly experiencing the traumatic event,*
>
> *2. witnessing, in person, the event as it occurred to others,*
>
> *3. learning that the traumatic events occurred to a close family member or close friend,*
>
> *4. experiencing repeated or extreme exposure to aversive details of the traumatic event*[1]*."*

[1] Does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related

The experience of such traumatic events has been associated with marked alterations in numerous biological and psychological processes known to play a vital role in the etiology of mental disorders.

1.2 Biological and psychological processes following trauma exposure

It is evident that the experience of extreme adversities can lead to intense immediate stress reactions. This initial reaction can include subjective feelings of fear, helplessness and horror, but also dissociative symptoms (APA, 2013, Maercker, 2013). Moreover, trauma-exposed individuals usually show a strong peri-traumatic autonomic and endocrine biological stress response (Chou, La Marca, Steptoe, & Brewin, 2014). In addition to these initial reactions, there is also broad evidence for persistent changes in the aftermath of traumatic events. Table 1 gives an overview of different persistent biological and psychological changes associated with traumatic event exposure (for more comprehensive reviews see Ryan et al., 2016; Schmidt et al., 2013; Zoladz & Diamond, 2013. Since the majority of these processes play a vital role in the etiology of mental disorders, they are assumed to mediate the effect of traumatic event exposure on the development of trauma-related psychopathology (Figure 1).

Table 1: Overview of changes in biological and psychological processes following traumatic events

Process	Examples	References
Biological		
HPA axis	Hypocortisolism; lower tonic and higher phasic levels; increased GR sensitivity; increased CRH	Baker et al., 1999; Rohleder et al., 2004; Schalinski et al., 2015; Steudte et al., 2013
SAM	Sympathetic hyperreactivity; elevated NA plasma levels; reduced parasympathetic tone	Scheeringa, Zeanah, Myers, & Putnam, 2004; Strawn & Geracioti, 2008; Yehuda et al., 1998
Startle Response	Exaggerated startle response	Guthrie & Bryant, 2005
Brain morphology	Reduced volume of hippocampus, anterior cingulate cortex, medial frontal gyrus	De et al., 2002; Rauch et al., 2003; Woodward et al., 2006
Brain function	Amygdala hyperresponsivity; lower PFC activity	Dannlowski et al., 2012; Lanius et al., 2001
Immune system	Inflammation, altered immune cell distribution	Baker, Nievergelt, & O'Connor, 2012; Sommershof et al., 2009
Epigenetics	Hypo-/Hypermethylation; chromatin modifications; micro RNA changes	Ressler et al., 2011; Snijders et al., 2017; Uddin et al., 2010
Microbiome	Decreased abundance of several bacteria; altered phylogenetic composition	Hemmings et al., 2017; Howard et al., 2017
Psychological		
Attentional processes	Attentionbal biases to emotional stimuli; Impaired attentional control	Aupperle, Melrose, Stein, & Paulus, 2012; Bar-Haim et al., 2010
Emotion regulation	Impaired reappraisal; increased suppression; experiential avoidance	Ehring & Quack, 2010; Shepherd & Wild, 2014
Memory	Autobiographic memory impairments; increased memories of emotional cues	Kleim, Ehring, & Ehlers, 2012; Mickley Steinmetz, Scott, Smith, & Kensinger, 2012
Learning	Enhanced fear conditioning, impaired safety signal learning	Orr et al., 2000; Peri, Ben-Shakhar, Orr, & Shalev, 2000
Executive functions	Reduced inhibitory control; impaired cognitive flexibility; context-driven control adjustments	Barrera-Valencia et al., 2017; Olff et al., 2014; Steudte-Schmiedgen et al., 2014
Reward processing	Sensitization of reward systems	Field & Quigley, 2009; Spanagel et al., 2014

HPA axis = hypothalamus-pituitary adrenal axis; GR = glucocorticoid receptor; CRH = glucocorticoid releasing hormone; SAM = sympathetic adrenomedullary system; NA = noradrenalin; PFC = prefrontal cortex; RNA = ribonucleic acid

1.3 Trauma exposure and mental disorders

The exposure to traumatic events is associated with a higher risk for a variety of mental disorders (Figure 1). These associations were primarily shown in cross-sectional, but also in several large scale longitudinal studies suggesting that mental disorders can actually be seen as sequeale of traumatic events and not only result from a higher probability of traumatic event exposure in indivuduals with mental disorders (e.g. living in a more dangerous environment). The most prominent trauma-related disorder is posttraumatic stress disorder (PTSD), which requires exposure to a traumatic event as a diagnostic criterion. Core features of PTSD are intrusions (involuntary, stressful memories) of the traumatic events, emotional numbness and avoidance, increased arousal and significant alterations in cognition and mood (e.g. distorted feelings like guilt or blame) (APA, 2013). In addition to PTSD, particularly strong associations with traumatic events can be found for problematic substance use patterns (e.g. harmful use) and substance use disorders. Individuals with a history of traumatic events have a higher probability of binge drinking, drinking above recommended thresholds, cannabis use, use of other illegal substances, alcohol use and substance use disorders (Debell et al., 2014; Hyman & Sinha, 2009; Stewart, 1996). Both PTSD and substance use disorders are severerly disabling mental health conditions assiated with tremendous individual and sociatel costs (Kessler, 2000; Rehm et al., 2009).

Beyond PTSD and substance use disorders, traumatic event exposure is also associated with anxiety (e.g. panic disorder) (Asselmann, Wittchen, Lieb, Perkonigg, & Beesdo-Baum, 2017) and mood disorders (e.g. major depression) (Maercker et al., 2004), sleep disorders (Pietrzak et al., 2010), psychotic disorders (Morrison, Frame, & Larkin, 2003) and personality disorders (Zanarini et al., 1997). Interestingly, there is not only evidence for a higher risk of mental disorders following traumatic events but also for a higher probability of treatment resistance in trauma-exposed individuals (Alden, Taylor, Laposa, & Mellings, 2006; Nanni, Uher, & Danese, 2012). This accumulating evidence for adverse mental health consequences has stimulated the development

of numerous interventions to prevent adverse mental health consequences following traumatic events.

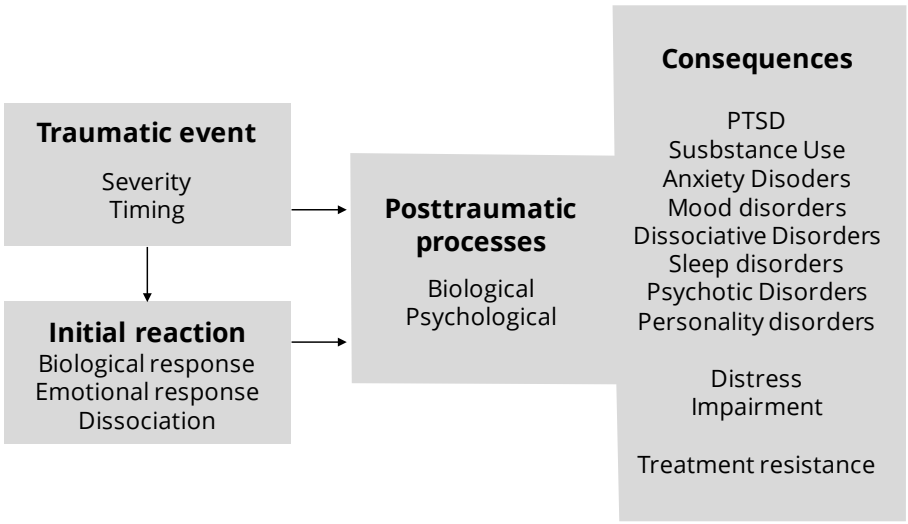

Figure 1: Initial reaction, posttraumatic processes and mental health consequences in a multifactorial framework model of trauma-related disorders (based on Maercker, 2013)

1.4 Efficacy of early interventions in the afternmath of trauma exposure

In the last two decades, various psychological and pharmacological early interventions have been developed to prevent the adverse effects of trauma exposure on mental health (see Linares et al., 2017 for a comprehensive overview). Psychological interventions include psychological debriefing (brief counseling within hours after the traumatic event, typically in groups) (Deahl et al., 2000), self-help information and psychoeducation (Bugg, Turpin, Mason, & Scholes, 2009), memory structuring interventions (Gidron et al., 2001), cognitive behavioral interventions (Bryant et al., 1999), as well as novel developments such as visuo-spacial tasks (Iyadurai et al., 2017). Pharmacological interventions include benzodiazepines (Gelpin, Bonne, Peri, Brandes, & Shalev, 1996), selective serotonin reuptake inhibitors (Suliman et al., 2015), propranolol (Pitman et al., 2002), glococorticoids (Schelling et al., 2006), morphines (Bryant et al., 2009) and ketamine

(Schönenberg, Reichwald, Domes, Badke, & Hautzinger, 2005). Although pre-clinical and clinical efficacy trials show promising results for several interventions such as cognitive behavioral treatments and administration of clucocorticoids (Kliem & Kröger, 2013; Sijbrandij, Kleiboer, Bisson, Barbui, & Cuijpers, 2015), the effect sizes are moderate at best. Many early interventions have no preventive (Hoskins et al., 2015; Kearns, Ressler, Zatzick, & Rothbaum, 2012; Linares et al., 2017; Sijbrandij et al., 2015) or even adverse effects (e.g. for psychological debriefing) (Rose, Bisson, Churchill, & Wessely, 2002).

An important reason for the limited efficacy of early intervention is the fact that these interventions are usually universally applied to trauma-exposed individuals. Despite the well-known association between traumatic events and psychopathology (see paragraph 1.3), epidemiological research also suggests that only a minority of trauma-exposed individuals will develop adverse mental health consequences (Breslau, 2009). This limits the potential efficacy of universal preventive efforts even if they target the pathological mechanisms. Thus, a major challenge in trauma research is to “clarify who needs intervention in the aftermath of trauma versus who will recover spontaneously.” (Kearns et al., 2012). An important first step in this direction is to estimate the proportion of trauma-exposed individuals that develops trauma-related disorders and how many stay resilient. If only a small proportion of individuals develop mental disorders following trauma exposure, it clearly suggests the relevance of moderating factors (Figure 2).

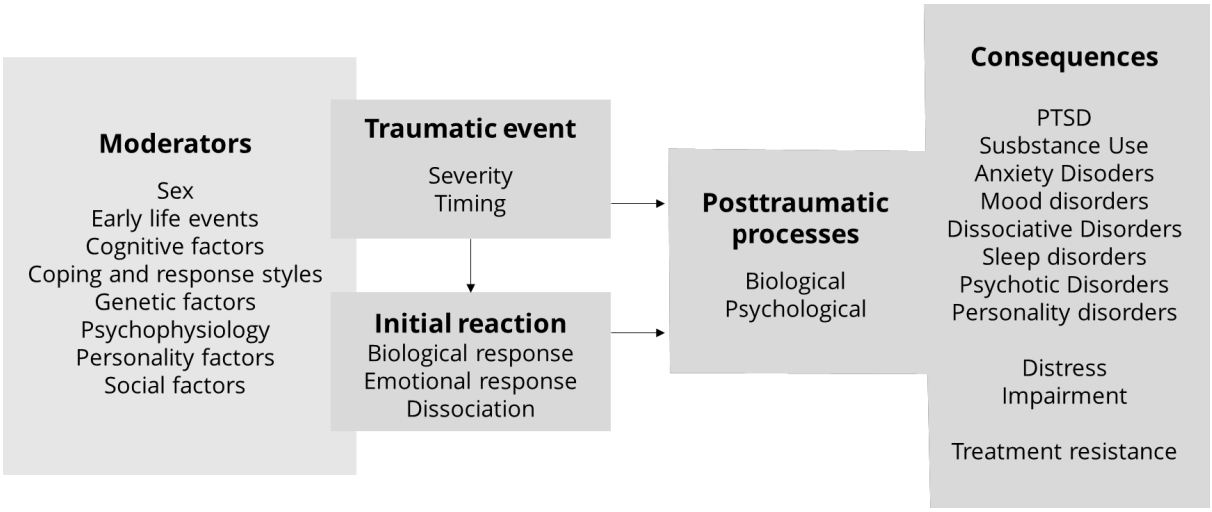

Figure 2: Initial reaction, posttraumatic processes, mental health consequences and moderating factors in a multifactorial framework model of trauma-related disorders (based on DiGangi et al., 2013; Maercker, 2013)

1.5 Moderating factors

Almost 20 years ago, two important meta-analyses already discussed potential factors that might be able to predict who is at risk for mental disorders after trauma exposure, and who remains resilient (Brewin, Andrews, & Valentine, 2000; Ozer, Best, Lipsey, & Weiss, 2003). Since then, theoritcal and methodological advancements in the past two decades have led to the identification of various promising candidates, which could improve the prediction of trauma-related mental disorders – and therefore the identification of individuals that might benefit from early interventions. Table 2 gives an overview of potential moderating factors reported in the literature. Because of the large number of putatively relevant variables, investigations of moderators should focus on factors that are likely to have a large impact on the risk of trauma-related disorders. A useful indicator for this impact of potential moderating variabels is their association with the severity of initial responses after trauma exposure (see. Figure 2).

Table 2: Candidates for factors moderating the risk of mental disorders following trauma exposure

Factor	Variant with higher risk	References
Sex	Female sex	Kessler et al., 1995
Early life events	Higher number of childhood adversities	Cabrera, Hoge, Bliese, Castro, & Messer, 2007
Psychopathology	History of pre-trauma mental disorders	LeardMann et al., 2009
Cognitive factors		
Intelligence	Decrased	Breslau, Chen, & Luo, 2013
Retrieval of autobiographical memories	Impaired	Bryant et al., 2007
Negative appraisals about self	Increased	Bryant & Guthrie, 2007
Processing speed	Impaired	Parslow & Jorm, 2007
Verbal ability	Impaired	Orr et al., 2012
Attention towards emotional stimuli and attention control	Mixed findings	Beevers et al., 2011; Schäfer et al., 2016
Coping and response styles		
Rumination	Increased	Nolen-Hoeksema & Morrow
Avoidance	Increased	Gil & Caspi, 2006
Difficulties in emotion regulation	Increased	Bardeen et al., 2013
Psychophysiology		
Startle Response	Increased	Guthrie & Bryant, 2005
EMG response	Increased	Guthrie & Bryant, 2006
Heart rate	Mixed	Buckley et al., 2005; Shalev et al., 1998
Basal cortisol	Decrased	Delahanty, Raimonde, & Spoonster, 2000
Glucocorticoid receptor	Higher number and sensitivity	van Zuiden et al., 2011, 2012
Personality factors		
Self-efficacy	Decrased	Heinrichs et al., 2005
Hostility	Increased	Heinrichs et al., 2005
Hardiness	Decrased	Thomassen et al., 2018
Trait-anxiety	Increased	Schweizer et al., 2017
Social factors		
Environment	Stressful environment	Boney-McCoy & Finkelhor, 1996
Social support	Decreased	Pietrzak et al., 2009
Socioeconomic status	Lower	Brattström, Eriksson, Larsson, & Oldner, 2015
Genetic factors		
CRHR1	Various SNPs	White et al., 2013
FKBP5	rs9470080 T allele	Binder et al., 2008
DRD2	Various SNPs	Dragan & Oniszczenko, 2009
DRD4	L allele	Voisey, Young, Lawford, & Morris, 2014
5-HTT	S allele	Koenen et al., 2011
ADCYAP1R1	C allele in females	Ressler et al., 2011

EMG = electromyogram; SNP = single nucleotide polymorphism
For comprehensive reviews see DiGangi et al., 2013; Ryan et al., 2016; Zoladz & Diamond, 2013

1.6 Initial response after trauma exposure

The abovementioned early reviews of risk factors for trauma-related mental disorders (Brewin et al., 2000; Ozer et al., 2003) suggested that the initial responses during and immediately after trauma exposure are among the most impotant predictors of psychopathological reactions. In fact, this was confirmed by numerous studies showing that long-term changes and trauma-related disorders could be predicted by initial emotional reactions (Marmar et al., 2006), negative cognitions (Laposa & Rector, 2012), dissociation (Birmes et al., 2003), and physical reactivity (Chou et al., 2014). Given this crucial role of initial responses after trauma exposure for the risk of psychopathology, the search for important moderating factors of adverse trauma-related consequences might be guided by concentrating on variables that are related to psychological and biological reactivity after stressful experiences. Well-known candidates for such variables include personality traits (Xin et al., 2017), early adverse life events (Loman & Gunnar, 2010), functioning of stress systems (Cribbet, Williams, Gunn, & Rau, 2011; Kao, Doan, John, Meyer, & Tarullo, 2018), and genetic factors (Ising & Holsboer, 2006).

1.7 Aims

The studies summarized in this thesis aimed at

(1) providing estimates on the prevelance of traumatic event exposure and trauma-related mental disorders for the general population and high-risk populations in which early interventions are frequently applied (*chapters 2 and 3*)
(2) investigating moderators of adverse mental health consequences following traumatic event exposure (*chapters 4 to 8*).

Chapter 2 summarizes epidemiological research from national and cross-national studies on the prevalence of traumatic events as well as the prevalence and conditional prevalence (prevalence among those exposed to a traumatic event) of PTSD in Europe, also including high-risk

populations from former war areas. Chapter 3 presents a study, which compared the prevalence of mental disorders in German soldiers after a military mission in Afghanistan (another potential high-risk population) with a sociodemographically matched general population sample.

Chapters 4 to 8 present different studies investigating moderators of adverse mental health consequences following traumatic events. As stated above (paragraph 1.6), these investigations focused on potential moderators that are likely to affect the severity of initial repsonses after trauma exposure as a major risk factor for adverse consequences. The following potential moderators were investigated:

(i) the susceptibility to others' emotions (i.e. emotional contagion)
(ii) childhood traumas
(iii) biological stress markers
(iv) specific genetic polymorphism involved in the degradation of monoamines (i.e. monoamine oxidase A gene)

The studies also investigated differenct outcomes relevant in the processing of traumatic events (see figure 2) including the initial affective and biological reaction, mental disorder symptoms (focusing on PTSD and alcohol use symptoms) and treatment response. To facilitate the orierentation in the following chapters, figure 3 shows a matrix where different moderators and outcomes are allocated to the studies presented in chapters 4 to 8.

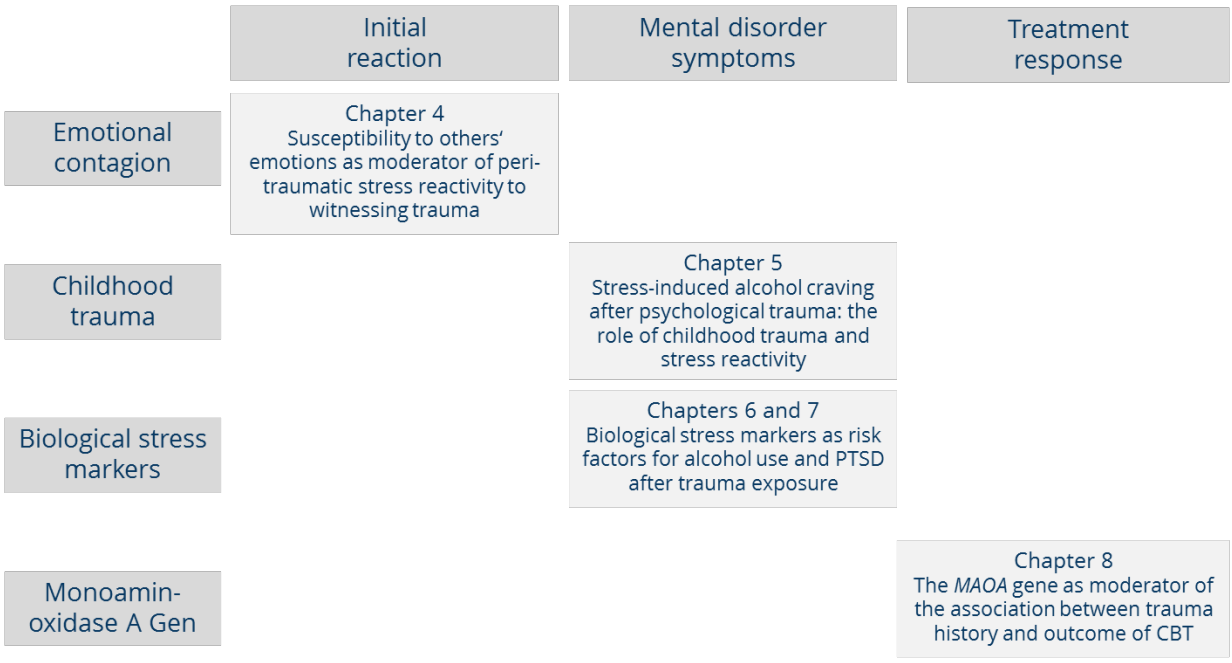

Figure 3: Strucutre of chapters including investigations of moderating factors (chapters 4 to 8)

2 Post-Traumatic Stress Disorder in Europe

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Trauma and PTSD in Europe

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INTRODUCTION

Until recently, epidemiological data on the prevalence and traumatic events and posttraumatic stress disorder (PTSD) have largely been based on studies and study groups from North America. The European research landscape is traditionally more fragmented with many smaller-scale regional or national studies. These studies only allow conclusions about specific samples and make it impossible to draw an accurate picture for the entire European continent. Fortunately, during the past two decades and increasing number of general population studies have become available for many countries that allow making assumptions about the prevalence of traumatic events and PTSD for Europe. Nevertheless, to integrate the existing findings from different European countries into an overall picture remains quite challenging. There is considerable variability in the methodology used across different studies in terms of sampling methods, considered age ranges, assessment instruments, timeframes and definitions of diagnostic thresholds. Moreover, the vast majority of European studies stems from a limited number of countries which makes it difficult to make valid estimations for the entire European population.

The current chapter mainly refers to two cross-national initiatives that tried to overcome these methodological obstacles. Presenting findings from these cross-sectional initiatives, we give an overview of the epidemiology of trauma and PTSD for Europe. In addition to providing figures for entire Europe, we expand on cross-national variation in PTSD prevalence including a discussion of possible reasons. We also present data from national population-based studies when the information of interest is not available from cross-national initiatives. This includes findings on trauma and PTSD from longitudinal population-based studies of which only a very limited number are available for European countries so far. Finally, we present findings on the epidemiology of PTSD in two populations in Europe that differ in

exposure to number and types of traumatic events: (1) former conflict area and (2) military populations.

CROSS-NATIONAL STUDIES

There have been two main cross-national initiatives that tried to overcome the limitations of national and regional studies described above. Both have become the best available benchmark in terms of cross-national descriptive epidemiology. The most important one is the WHO World Mental Health (WMH) Surveys Initiative. This initiative, which has already been introduces in the previous chapter, is a series of general population studies carried out in 28 countries throughout the world between 2001 and 2012 (Kessler et al. 2009; Kessler and Ustun 2008). Some of these studies were conducted in European countries, of which the majority (Belgium, France, Germany, Italy, Netherlands and Spain) were summarized in the European Study of the Epidemiology of Mental Disorders (ESEMeD) project (Alonso et al. 2002). All studies in the WMH Surveys Initiative used the same diagnostic interview (Composite International Diagnostic Interview, Kessler & Ustün, 2004) making diagnoses comparable across studies. Detailed sampling and weighting schemes also allow for a better integration of national data and more reliable estimates of disorder prevalence and correlates across countries. The assessment methods of the WMH surveys also allowed a more unbiased estimate of trauma exposure and of the conditional probability of PTSD by not only considering the worst lifetime trauma (causing upward bias of conditional PTSD risk) but also a random trauma (also see previous chapter for a detailed description).

Another initiative that aimed at deriving estimates across European countries was coordinated by the European Brain Council (EBC) and the European College of Neuropsychopharmacology (ECNP) (Wittchen and Jacobi 2005; Wittchen et al. 2011). This initiative was launched in 2003 (and updated in 2010) and consisted of re-analyses of national data sets from individual epidemiological studies in the European Union (EU), partly also

incorporated findings from the above WMH/ESEMED consortium. Moreover, expert consultations were considered to allow the calibrations of estimates for countries with few available epidemiological data. Although these two large initiatives are not able to fully solve the problems mentioned above, they allow quite accurate estimations of prevalence and characteristics of traumatic events and PTSD across European countries.

PREVALENCE OF TRAUMATIC EVENTS

The ESEMeD project is – to our knowledge - the only study providing cross-national estimates for the prevalence of traumatic events in Europe (Darves-Bornoz et al. 2008). According to these data, 63.6% (95% CI = 61.6–64.8) of all individuals experience at least one traumatic event in their lives, with men being exposed slightly more often than women (67.0% vs 60.5%). The mean number of traumatic experiences is 1.5 (SD=2.8) in the overall population and 2.4 (SD=2.6) among individuals with at least one traumatic event. Moreover, compared to individuals without trauma exposure, those who were exposed are more likely to be older than 65 years (24.1% vs 14.7%), to be retired (27.4% vs 16.8%), to live in a large city (30.7% vs 23.5%) and to be separated, widowed or divorced (12.7% vs 8.4%).

There is a large variability in the probability of different traumatic events. While some events such as unexpected death of a loved one (24.6%), witnessing death or seeing persons seriously hurt (20.6%), automobile accidents (11.7%), or life-threatening illnesses (10.5%) occur with a high probability, other events like seeing atrocities (2.3%), being raped (1.6%), being kidnapped (0.8%), or purposely killing, torturing or injuring someone (0.4%) are experienced very rarely. The prevalence of trauma exposure appears to be lower in Europe as compared to the United States for most traumatic events (Benjet et al. 2015) (see Table 1) with, however, considerable variation across European countries which will be discussed later.

Table 1. Prevalence of traumatic events in European countries in the WMH surveys

	Any collective violence	Any caused/ Witnessed bodily harm	Any interpersonal violence	Any intimate partner/ sexual violence	Any accidents or injuries	Any other trauma	Total with any event
	% (SE)	% (SE)	% (SE)	% (SE)	% (SE)	% (SE)	% (SE)
Portugal	7.5 (0.8)	23.9 (1.3)	20.0 (1.3)	15.8 (1.2)	41.2 (1.5)	33.5 (1.5)	69.0 (1.7)
Spain	7.0 (0.7)	8.7 (1.0)	3.8 (0.6)	7.7 (0.7)	28.5 (1.4)	32.0 (1.6)	54.0 (1.7)
France	14.8 (1.9)	29.3 (1.8)	4.6 (0.6)	22.0 (1.4)	36.0 (2.0)	38.3 (1.8)	72.7 (2.3)
Northern Ireland	24.3 (1.3)	21.7 (1.2)	12.6 (1.1)	18.3 (0.9)	22.8 (1.3)	34.9 (1.3)	60.6 (1.7)
Netherlands	12.6 (1.8)	21.7 (1.6)	6.1 (0.9)	20.3 (1.9)	28.2 (1.9)	38.6 (2.8)	65.6 (2.8)
Belgium	15.3 (2.0)	20.6 (2.0)	6.2 (0.9)	20.5 (2.3)	32.2 (2.6)	34.5 (2.6)	65.8 (3.1)
Germany	14.7 (1.3)	25.1 (1.3)	9.3 (1.0)	20.7 (1.5)	32.2 (1.8)	34.1 (2.2)	67.3 (2.2)
Ukraine	15.0 (1.3)	28.8 (1.9)	20.6 (1.8)	29.9 (1.8)	52.5 (1.7)	49.5 (2.2)	84.6 (1.7)
Romania	3.1 (0.4)	12.0 (0.8)	7.5 (0.7)	8.1 (0.8)	26.4 (0.9)	13.9 (1.0)	41.5 (1.1)
Bulgaria	0.4 (0.2)	7.1 (0.7)	1.2 (0.3)	6.6 (0.6)	16.1 (1.2)	12.6 (1.1)	28.6 (1.3)
Italy	6.9 (0.7)	25.8 (2.2)	4.1 (0.6)	11.3 (0.9)	27.9 (1.9)	24.3 (1.4)	56.1 (2.2)
USA	6.8 (0.4)	31.3 (0.8)	21.4 (0.9)	69.9 (1.4)	50.6 (1.3)	52.1 (1.2)	82.7 (0.9)

Adapted from Benjet et al. (2015)
WMH = World Mental Health

PREVALENCE OF PTSD

Although the majority of European individuals are exposed to at least one traumatic event during their lives, only small proportion develops a PTSD. The ESEMeD project found a lifetime prevalence of 0.9% for males and 2.9% for females across six European countries (Belgium, France, Germany, Italy, Netherlands and Spain). The 12-month prevalence was estimated at about half the lifetime prevalence with 0.4% for males and 1.3% for females (Alonso et al. 2004c). The 12-months prevalence of PTSD in the entire EU is estimated to lie between 1.1% and 2.9% (Wittchen et al. 2011). These figures are lower than those in the United States (see previous chapter) (Kessler et al. 2005; Goldstein et al. 2016) and comparable to those in Australia (12-month prevalence: 1.3% for males, 1.6% for females, assessment methods differ compared to the WMH surveys) (Rosenman 2002). The conditional PTSD risk (risk of PTSD in case of trauma exposure) varies massively between types of traumatic events. The strongest associations to PTSD development can be found for being kidnapped (OR 9.8), being raped (OR 8.9), being beaten by spouse or romantic partner

(OR 7.3), undisclosed private events (OR 5.5), accidentally caused serious injury or death (OR 5.2) and having a child with serious illness (OR 5.1).

No cross-national longitudinal study has been conducted in Europe so far. National population-based longitudinal studies that include estimates of PTSD prevalence are also extremely scarce with only two studies being available to date. The largest and most comprehensive longitudinal study was conducted in Germany among adolescents and young adults aged 14-24 years who were followed up to ten years (Beesdo-Baum et al. 2015). The diagnostic interview used in this study was largely comparable to the WMH survey with the important difference that PTSD was assessed based on the worst trauma method only (see above). This study found a low 12-month prevalence of 1.2% in women and 0.1% in men (Perkonigg et al. 2000) at baseline. About half of all PTSD cases remitted during the follow-up period, with new traumatic events being the strongest predictor of a chronic course (Perkonigg et al. 2005). The second longitudinal study was conducted in an adult general population sample in Switzerland using a two-phase diagnostic assessment with an initial screening and a subsequent diagnostic interview (Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology, SPIKE, Angst and Dobler-Mikola 1985) applying DSM-III and DSM-IV criteria. The 12-month prevalence of PTSD was published for the last two follow-up assessments and strikingly, none of the participants met the full PTSD criteria. The authors attributed this observation to the absence of warfare in the past 150 years and a very low rates of trauma exposure in general as well as for trauma types with high impact such as interpersonal and disasters (Hepp et al. 2006). These two longitudinal studies conducted in national restricted samples allow only limited conclusions about the course of PTSD for Europe.

DISABILITY AND IMPACT OF PTSD

Although the prevalence estimates for PTSD in Europe seem also quite low compared to other mental disorders, it still means that, in absolute numbers, about 7.7 million people in the EU are affected by PTSD within any given year (Wittchen et al. 2011). This is a considerable size considering the severity and impact of the disorder. It is noteworthy that PTSD is highly comorbid with other mental disorders. The proportion of comorbid disorders among individuals with 12-month PTSD is 57.9% and the disorders most strongly related to PTSD are major depression (OR 20.7), panic disorder (OR 17.6), general anxiety disorder (OR 15.1) and agoraphobia (OR 12.5) (Alonso et al. 2004a). This might be one reason for the high levels of disability associated with PTSD. The ESEMeD project assessed work loss days and both mental and physical quality of life (Alonso et al. 2004b). PTSD was among the mental disorders with the highest work loss days index (composition of answers to three questions whether subjects were (1) totally unable to work, (2) had to cut down work or (3) had to cut back the quality of work because of problems with either your physical health in the past 30 days, question (1) was double-weighted). However, when comorbidity was taken into account, PTSD was only moderately associated with work loss days (OR 2.1) compared to other mental disorders (ORs 1.2-3.3) indicating that high number of work loss days occurring in individuals with PTSD could indeed be partially explained by comorbidity. Is also noteworthy that PTSD was the only mental disorder that had comparable negative impact on both mental and physical quality of life reflecting the string relationships between PTSD and physical morbidity such as (chronic musculoskeletal pain, hypertension, hyperlipidaemia, obesity and cardiovascular disease) (McFarlane 2010).

Beyond these individual consequences of PTSD, there are also considerably societal consequences in terms of healthcare costs (direct costs) and productivity losses (indirect costs). These costs were estimated for the EU within the EBC/ECNP initiative (Gustavsson et

al. 2011). According to these estimates, each of the 7.7 million individuals affected by PTSD in a given year cause costs in the amount of 1082 Euro in that year, summing up to 8.385 billion Euro per year caused by healthcare costs and productivity losses due to PTSD.

CROSS-NATIONAL VARIATION IN PTSD PREVALENCE

Although the European continent is quite homogeneous with most nations being classified as middle- and high-income countries (World Bank), there is still a large variability in the prevalence of PTSD. Table 2 shows the 12-month prevalence of DSM-IV PTSD for European countries that participated in the WMH surveys (Karam et al. 2014). The 12-month prevalence varies considerably between 0.4% in Spain and 3.8% in Northern Ireland. A relatively high prevalence can also be found in the Ukraine (2.0%), while prevalence rates in other Eastern European countries are much lower. The conditional risk of PTSD development (prevalence of PTSD among those with traumatic event exposure) corresponds to these figures with the highest rate (17.6%) in Northern Ireland and much lower rates in Italy, Spain (both approx. 3.5%) (Ferry et al. 2014; Carmassi et al. 2014; Olaya et al. 2014) and France (2.9%) (Husky et al. 2015). Although a large population-based survey is also available for England, the reported prevalence of PTSD of 2.3% in men and 3.3% in women is not comparable to the figures presented above since the English survey used a screening tool (Trauma History Questionnaire) to estimate the presence of current PTSD (MacManus et al. 2009).

Demographic correlates of PTSD also vary between European countries with gender being the only cross-national demographic correlate of PTSD (Darves-Bornoz et al. 2008). Low education is related to PTSD risk in Italy (Carmassi et al. 2014), age under 65 years, being retired or unemployed in Northern Ireland (Ferry et al. 2014), age over 60 years in Germany (Maercker et al. 2008), being unmarried or divorced in The Netherlands (Bronner et al. 2009) and being foreign-born in Sweden (Frans et al. 2005).

Table 2: Prevalence of 12-month PTSD in European countries in the WMH surveys

	%	SE
Spain	0.4	0.1
France	1.4	0.3
Northern Ireland	3.8	0.5
Netherlands	1.2	0.3
Belgium	0.6	0.1
Germany	0.5	0.2
Ukraine	2.0	0.4
Romania	0.4	0.2
Bulgaria	0.9	0.2
Italy	0.4	0.1

Adapted from Karam et al. (2014)
WMH = World Mental Health, SE = standard error

It is important to consider that reliable data on the prevalence of PTSD does not exist for all European countries. Although the majority of European countries is largely comparable in terms of culture, living arrangements and income, the available data from the WMH surveys shows considerable variance in trauma prevalence between countries suggesting that existing findings might not generalized to countries for which no data is available. This particularly applies to countries which encounter circumstances that might contribute to a higher PTSD risk. A good example is Greece which has a severe economic crisis since 2009 which has massively affected employment, income and access to health care (Kentikelenis et al. 2014). Some effects of these changes on mental health have already been documented (Simou and Koutsogeorgou 2014), but population-based data on the prevalence of PTSD in Greece is still lacking. So although the existing cross-national initiatives covered many European countries, there are still many blind spots for which systematic data on the epidemiology of PTSD is needed.

The reasons for the observed differences in prevalence rates of PTSD across European countries are difficult to determine. The factor that is most likely to contribute to these differences is the considerable variation in the occurrence of type and number traumatic events as a consequence of historical, cultural, and political factors (Atwoli et al. 2015). As

shown in Table 1, countries with a higher PTSD prevalence also tend to have higher exposure rates for traumatic events in general or at least for specific events (Benjet et al. 2015). For example, Bulgaria (28.6%) and Romania (41.5%) have the lowest rates of exposure to any event. The highest rates of exposure were found for Ukraine (84.6%). This might be at least partially attributable to the Chernobyl accident which is reflected in high rates of accidents or injuries and man-made disasters. Another example is Northern Ireland, the European country with the highest PTSD prevalence in the WMH surveys. As a consequence of civil conflicts, Northern Ireland has particularly high rates of exposure to collective violence, an event type with a high impact (Bunting et al. 2013). This is also reflected in the high conditional PTSD prevalence rate in Northern Ireland (Ferry et al. 2014).

European countries do not only differ regarding the probability of trauma exposure in general but also regarding specific traumatic events. The most important difference is probably the exposure to war. This does mainly apply to World War II, but also to more recent conflicts such as the Balkan war (discussed separately below). Seven decades after World War II, the number of individuals that were directly exposed is relatively small. However, there is still evidence that countries with many war victims (e.g. The Netherlands and France) tend to have higher PTSD rates compared to countries with fewer war victims (e.g. Spain and Italy) (Burri and Maercker 2014) (see Table 3). This observation can be explained by the fact that the consequences of war are not limited to direct exposure but can also influence the odds of developing PTSD by indirect consequences (e.g. childhood adversities in the aftermath of war) (Nemeroff 2016) and transgenerational effects of trauma exposure (e.g. through epigenetic mechanisms) (Yehuda and Bierer 2008).

Table 3: Prevalence of current PTSD in war victims in European countries

	PTSD Prevalence (%)	War victims*
Belgium	0.8	.007
France	2.3	.013
Germany	2.3	.009
Italy	0.7	.009
Netherlands	3.3	.014
Croatia	6.7	.100
Spain	0.6	.000
Switzerland	0.7	.000
UK	3.0	.009
Bulgaria	0.9	.002
Romania	0.4	.012

Adapted from Burri and Maercker (2014)
*In proportion to total inhabitants

Besides the differences in exposure to traumatic events, there is some evidence that cultural differences between European regions also contribute to variance in PTSD prevalence rates. For example, Burri and Maercker (2014) found that some value orientations (e.g. modern and traditional values) interact with country-specific trauma rates. It is also likely that there are cultural differences regarding whether individuals share parts of their traumatic experiences (disclosure) which was shown to be predict recovery from posttraumatic stress (Mueller, Moergeli, and Maercker 2008). Thus, these cultural factors might have an incremental value in the explanation of PTSD prevalence rates but are still barely considered in epidemiological research.

PTSD IN FORMER CONFLICT AREAS

After World War II, the majority of the European civilian population has not been directly exposed to war trauma. An exception are the Balkan countries which were involved in a series of violent conflicts between 1991 and 2001 in the territory of the former Yugoslavia (Nation 2003). These countries therefore deserve special attention when looking at PTSD in Europe. In the years 2005 and 2006, a cross-national study in randomly selected community samples was conducted including samples from Bosnia-Herzegovina, Croatia, Kosovo, the Republic of

Macedonia, and Serbia (Priebe, Bogic, Ajdukovic, et al. 2010; Priebe, Bogic, Ashcroft, et al. 2010; Priebe et al. 2013). This study used a different diagnostic interview (Mini–International Neuropsychiatric Interview, MINI) than the WMH surveys (Composite International Diagnostic Interview, CIDI). However, there is evidence for a good concordance between the PTSD diagnoses obtained from both instruments suggesting that prevalence rates should be largely comparable (Lecrubier et al. 1997).

Table 4: Prevalence of current PTSD in war-affected Balkan countries

	%	SE
Bosnia and Herzegovina	35.4	1.9
Croatia	18.0	1.4
Kosovo	18.2	1.5
Republic of Macedonia	10.6	1.2
Serbia	18.8	1.6

Adapted from Priebe et al. (2010)
SE = standard error

In 2006, PTSD rates were considerably higher in all war-affected Balkan countries compared to other European countries with, however, large variations across Balkan countries (Table 4). This is noteworthy since the Balkan countries share much of their history, culture, and traditions (Priebe, Bogic, Ajdukovic, et al. 2010). The by far highest PTSD prevalence was found in Bosnia-Herzegovina (current PTSD: 35.4%), the lowest in Macedonia (current PTSD: 10.6%). The high prevalence of PTSD in Bosnia-Herzegovina corresponds to a high prevalence of several traumatic events during war such as being under siege (98.1%), lack of food or water (96.6%), lack of shelter (81.4%), and learning about murder or death of a dear person (69.0%). Across all Balkan countries, individuals being older (OR 1.02 per year), female (OR 1.5), having experienced more traumatic events during (OR 1.3) and after war (OR 1.2), and being unemployment (OR 1.7) had a higher PTSD risk (Priebe, Bogic, Ajdukovic, et al. 2010). It is noteworthy that a follow up study of all PTSD cases found that about one third no longer fulfilled the diagnostic criteria for PTSD one year later (S. Priebe et

al. 2013), indicating decreasing PTSD rates over time. However, findings in other war-affected populations suggest that PTSD rates are elevated even after more than a decade (Koenen et al. 2008) and that the short-term decreases observed in the Balkan area might rather reflect fluctuations in PTSD symptoms.

PTSD IN EUROPEAN MILITARY POPULATIONS

Unlike the majority of the European population, individuals serving in European military forces have been at risk for exposure to war-related trauma during deployment in military conflicts such as the wars in Kosovo, Iraq and Afghanistan. Thus, military populations deserve special attention when describing the epidemiology of PTSD in Europe. However, only a few systematic studies have been conducted in representative military samples in European countries. Most data comes from a large cohort study in a representative military sample in the United Kingdom which has by far the highest number of military personnel deployed in conflict areas (Hotopf et al. 2006; Fear et al. 2010). This study found a high probability for exposure to war-related events such as coming under mortar/artillery fire/rocket attack (77.6%), coming under small arms/RPG fire (50.2%) and seeing personnel wounded or killed (46.6%) among individuals deployed in Iraq or Afghanistan. The prevalence of current PTSD was estimated at 3.9% for men and 4.8% for women. It is important to note that like in the English general population survey (MacManus et al. 2009), the UK military study used a screening instrument (Posttraumatic Stress Disorder Checklist - Civilian Version) instead of clinical interviews to determine the prevalence of PTSD, probably overestimating its true prevalence. The probability of current PTSD was higher in reservists compared to regular personnel, did not differ between deployed and non-deployed personnel (Fear et al. 2010) and was roughly comparable to the general population (MacManus et al. 2009), although direct comparisons are restricted due to differences in methodology. Beyond the UK military, the only population-based study was conducted in

Germany (Wittchen et al. 2012) using the same clinical diagnostic interview that was used in the German longitudinal study described above (Beesdo-Baum et al. 2015). The German military study found lower probabilities for war-related events compared to the UK (coming under mortar/artillery fire/rocket attack (36.0%), coming under small arms/RPG fire (24.6%), seeing personnel wounded or killed (31.3%)) as well as a 12-month PTSD prevalence of 2.9%. Unlike in the UK study, deployed personnel had a higher probability for 12-month PTSD than non-deployed (OR 2.5). A direct matched comparison with a community survey found no differences in PTSD prevalence between German military personnel and the general population (Trautmann et al. 2016).

To summarize, the available data from population-based military studies conducted in UK and Germany suggest that despite considerable exposure to war-related events, the prevalence of PTSD in military personnel is comparable to the general population. These findings are supported by smaller studies from other European forces (Reijnen et al. 2014; Klaassens et al. 2008) and differ from the US military were a much higher probability of PTSD was observed (Hoge et al. 2004; Kessler et al. 2014). Possible explanations for a lower PTSD prevalence in European military populations are differences in direct combat exposure, demographic characteristics, cultural variables and risk factors for PTSD development (e.g. childhood maltreatment) (Hunt et al. 2014; Sundin et al. 2014; Trautmann et al. 2016).

SUMMARY

Exposure to traumatic events is common in Europe with about two thirds of the European population experiencing at least one traumatic event in their lives. However, only a small fraction of those exposed to a traumatic event develops a full PTSD diagnosis. Within a 12 month period, between 1 and 3% of the EU population are affected by PTSD which corresponds to about 7.7 million people. The PTSD prevalence varies considerably between European countries with differences in trauma exposure, war history, cultural factors and

health care systems as possible reasons. As the only European area with recent war exposure, Balkan countries have the highest PTSD prevalence ranging between 10 and 35%. Further research is needed to obtain representative data from European countries without national surveys as well as to elucidate the prevalence differences across European countries considering the influence of cultural factors.

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3 Prevalence and severity of mental disorders in military personnel and civilians

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ORIGINAL ARTICLE

Prevalence and severity of mental disorders in military personnel: a standardised comparison with civilians

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Aims. Provision and need for mental health services among military personnel are a major concern across nations. Two recent comparisons suggest higher rates of mental disorders in US and UK military personnel compared with civilians. However, these findings may not apply to other nations. Previous studies have focused on the overall effects of military service rather than the separate effects of military service and deployment. This study compared German military personnel with and without a history of deployment to sociodemographically matched civilians regarding prevalence and severity of 12-month DSM-IV mental disorders.

Method. 1439 deployed soldiers (DS), 779 never deployed soldiers (NS) and 1023 civilians were assessed with an adapted version of the Munich Composite International Diagnostic interview across the same timeframe. Data were weighted using propensity score methodology to assure comparability of the three samples.

Results. Compared with adjusted civilians, the prevalence of any 12-month disorder was lower in NS (OR: 0.7, 95% CI: 0.5–0.99) and did not differ in DS. Significant differences between military personnel and civilians regarding prevalence and severity of individual diagnoses were only apparent for alcohol (DS: OR: 0.3, 95% CI: 0.1–0.6; NS: OR: 0.2, 95% CI: 0.1–0.6) and nicotine dependence (DS: OR: 0.5, 95% CI: 0.3–0.6; NS: OR: 0.5, 95% CI: 0.3–0.7) with lower values in both military samples. Elevated rates of panic/agoraphobia (OR: 2.7, 95% CI: 1.4–5.3) and posttraumatic stress disorder (OR: 3.2, 95% CI: 1.3–8.0) were observed in DS with high combat exposure compared with civilians.

Conclusions. Rates and severity of mental disorders in the German military are comparable with civilians for internalising and lower for substance use disorders. A higher risk of some disorders is reduced to DS with high combat exposure. This finding has implications for mental health service provision and the need for targeted interventions. Differences to previous US and UK studies that suggest an overall higher prevalence in military personnel might result from divergent study methods, deployment characteristics, military structures and occupational factors. Some of these factors might yield valuable targets to improve military mental health.

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Key words: Epidemiology, mental health, military psychiatry, posttraumatic stress disorder.

Introduction

Mental disorders are strongly related to disability and premature death across various nations (Whiteford *et al*. 2013). The identification of individuals at high risk for mental disorder is crucial to adequately inform public policy and health care strategies. Numerous studies have shown high rates of common mental disorders such as posttraumatic stress disorder (PTSD), major depressive disorder and alcohol use disorders (AUD) in military personnel (Kang & Hyams, 2005; Gadermann *et al*. 2012; Sirratt *et al*. 2012; Wittchen *et al*. 2013). However, there is still debate on whether military personnel can be considered as a high risk population, compared with other populations (Hoge *et al*. 2014; Kessler *et al*. 2014*a*). Although stressors related to military service have been linked to an increased risk for mental disorders (Jones *et al*. 2000; Hoge *et al*. 2004; Browne *et al*. 2007), selection and retention criteria could facilitate the selection of resilient individuals. Moreover, there is evidence that only specific subsamples with high-risk exposures such as combat experiences, serious accidents and childhood adversities are

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at elevated risk for morbidity (Jones *et al.* 2013). In fact, some epidemiological studies suggest that rates of mental disorders in military personnel are comparable with those in the general population (Riddle *et al.* 2007; Klaassens *et al.* 2008; Fear *et al.* 2010). The interpretability of direct comparisons between military and general population studies, however, is restricted since methodology often differs between studies. Moreover, military samples are predominantly male, relatively young and by definition exclude unemployed individuals, which can lead to different prevalence estimates compared with the general population (Jacobi *et al.* 2014; Kessler *et al.* 2014*b*). Available data on mental disorders in comparable samples of soldiers and civilians using the same methodology is extremely limited. We are only aware of two studies that used comparable assessment methods as well as a rigorous calibration of military and civilian samples (by means of weighting procedures or statistical adjustments) taking at least differences in sex, age and employment status into account (Kessler *et al.* 2014*b*; Goodwin *et al.* 2015). The first found a generally higher risk for current mental disorders in a large representative US army sample compared with civilians (Kessler *et al.* 2014*b*). The second compared common mental disorders between UK serving military personnel and the general working population in the same age range and also observed higher rates in military personnel (Goodwin *et al.* 2015). These findings may not apply to other nations since there are cross-national differences in risk (e.g. experience of childhood adversities) and resilience factors (e.g. self-efficacy), but also in aspects of system culture (e.g. leadership) and perception of mental illness (e.g. stigmatisation). These factors might be related to mental health (Kessler *et al.* 1997; Maciejewski *et al.* 2000; Rüsch *et al.* 2005; Jones *et al.* 2012) and result in cross-national differences in rates of mental disorders found in military personnel (Hunt *et al.* 2014; Sundin *et al.* 2014). Moreover, it remains unclear whether the differences reported in the above-mentioned studies are attributable to military service in general or to previous deployments since comparisons were made with samples representative for the entire military including both previously deployed and never deployed soldiers (NS). This study presents data on the 12-month prevalence and severity of DSM-IV mental disorders from a sample of German DS, a comparable sample of NS and sociodemographically matched civilians.

Methods

Samples

Data for the DS and NS were taken from the Prevalence, Incidence and Determinants of Post Traumatic Stress and Other Mental Disorders-study (Wittchen *et al.* 2012*a*). The DS sample was drawn from a reference population of 9617 soldiers who were deployed to Afghanistan as part of the 20th and 21st contingents of the German International Security Assistance force (ISAF) mission in 2010. Power calculations indicated that sufficient determination of prevalence rates could be achieved with a 36% ($n = 3493$) sample of the total of 9617 soldiers, with assumed non-eligibility and refusal rates. The random sample was stratified, oversampling combat personnel as an assumed high-risk population. Of the 3493 DS, 1599 met eligibility criteria. To be classified as eligible, soldiers had to be at least 18 years old and had to be present at their home base location during the assessment periods. Moreover, only locations with a sufficient high number of eligible soldiers ($n = 50$) could be considered due to logistical and financial constraints. Examination of medical records revealed no evidence that non-eligible subjects differed from those being eligible regarding the prevalence of mental health problems (Wittchen *et al.* 2012*a*). Of all eligible soldiers, 102 refused participation, seven did not show up at the scheduled assessment and seven provided incomplete data. The final DS sample consisted of 1483 soldiers (response rate 92.8%). For the NS sample, 1758 soldiers were drawn from the same home base locations. Eligibility criteria were being at least 18 years old (as in the DS sample) and having never been deployed. From 932 soldiers being eligible, 40 refused participation and seven provided incomplete data. The final NS sample consisted of 889 soldiers (response rate 95.4%). For this study, all female soldiers (DS: 44, NS: 110) were excluded because these low numbers would not allow meaningful analyses.

For the civilian sample, a subsample was taken from the mental health module of the German Health Interview and Examination Survey for Adults, a representative examination of physical and mental health in the German adult general population (age 18–79). Design and methods of the mental health module of this survey are described elsewhere (Jacobi *et al.* 2013). A total sample of 8152 was drawn for the main survey from local population registries. For the mental health module, 6027 met the eligibility criteria (aged between 18 and 79, completed assessment in the main survey, informed consent for the mental health supplement, sufficient language skills, being available during the assessment period). Of all eligible subjects, 527 refused participation, 197 could not be scheduled for assessment and 820 provided only partial information, resulting in a sample of 4483 subjects (response rate 74.4%). To assure comparability with the military samples, females, individuals older than

57 years and those not currently employed were excluded making a subsample of 1023 civilians available for analyses. Further adjustment of these samples according to sociodemographic variables is described below.

Data collection

In the military study, data were collected by non-military trained interviewers, dispatched to soldiers' home bases. Soldiers were informed about the study approximately 2 months in advance to arrival of the study team via personal written invitation. Participation was strictly voluntary and confidential. All eligible soldiers were released from their routine duty irrespective of willingness to participate. Thus, participation was solely decided by the individual soldier directly before the scheduled interview without knowledge of their leaders. DS and NS were examined in parallel at their home bases. In the general population survey, interviews were conducted by clinically trained interviewers either at the respondent's home, at local study centres or at another place of the participant's choice if neither home or study centre were suitable. Interviews were conducted in strict confidentiality. All participants provided informed consent and the study procedure was approved by the TUD Ethics Board (EK 72022010).

Diagnostic assessment

The Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI) (Wittchen & Pfister, 1997) was used in both studies. The DIA-X/M-CIDI allows the standardised assessment of symptoms, syndromes and diagnoses according to the criteria of DSM-IV-TR (American Psychiatric Association, 2000). The reliability and validity of the study instrument has been demonstrated in various studies (Lachner *et al.* 1998; Reed *et al.* 1998; Wittchen *et al.* 1998). For the purposes of this study we reported 12-month internalising disorders and substance use disorders (SUD), of which some disorders were grouped together because of small case numbers. Internalising disorders included panic disorder/agoraphobia, PTSD, phobias (social phobia, specific phobia, other anxiety disorders (obsessive compulsive disorder (OCD), generalised anxiety disorder (GAD)) major depressive disorder and bipolar disorder. SUD included alcohol abuse, alcohol dependence and nicotine dependence. Other disorders were either not assessed (e.g. attention-deficit/hyperactivity disorder, intermittent explosive disorder) or were too rare in at least one of the studies to permit meaningful analyses (e.g. psychotic disorders, SUD related to illicit or prescribed substances) (Wittchen *et al.* 2013; Trautmann *et al.* 2014).

Sociodemographic and military career variables

Sociodemographic variables that were assessed in both studies were age, marital status (married, unmarried), and education (low: 8th grade, middle: 10th grade, high: high school). Military career variables considered here to describe the military samples included rank (enlisted, non-commissioned officer, commissioned officer), unit (combat, medical, combat support) and number of deployments. The distributions of sociodemographic variables for the DS, NS and the civilian sample are shown in Table 1. For more detailed analyses in DS, the number of combat experiences was also assessed using the respective list of events of the Mental Health Advisory Team (Mental Health Advisory Team (MHAT IV), 2006) which includes 33 different events ranging from rather mild (e.g. seeing destroyed homes and villages) to severe events (e.g. being wounded or injured). DS experienced on average 6.9 (S.D. = 6.1) combat events. Detailed information on type and exposure for each single event is provided elsewhere (Wittchen *et al.* 2012*b*). DS were then categorised into DS with low combat exposure (three or less events, 38.2%) and DS with combat events (more than three events, 61.8%).

Severity of mental disorders

The presence of comorbid disorders and self-rated impairment (for internalising disorders), as well as the number of reported symptoms (for SUD), were used as measures of disorder severity. For the assessment of impairment, respondents rated how much their daily life and activities were impaired by the symptoms of the respective disorder on a five-point scale ranging from 0 (no impairment) to 4 (very severe impairment). This item was also used to represent the impairment criteria (at least moderate impairment) of several DSM diagnoses in the CIDI diagnostic algorithms. This resulted in a low variance of disorder severity. Thus, the threshold for impairment in the diagnostic algorithm was lowered (at least mild impairment) for all analyses including the severity of internalising disorders. The severity of AUD and nicotine dependence was defined as the total number of symptoms that were endorsed. This measure of severity of SUD is in accordance with the approach that was introduced in DSM-5 (Hasin *et al.* 2013).

Table 1. *Distribution of sociodemographic and military career variables in DS, NS and civilians*

	Military						Civilians		
	Deployed			Never deployed					
	(*n* = 1439)			(*n* = 779)			(*n* = 1023)		
	n	%	%w*	*n*	%	%w*	*n*	%	%w*
Demographic									
Age									
<25	383	26.6	19.4	423	54.3	27.8	82	8.0	19.7
25–29	537	37.3	37.1	237	30.4	37.1	82	8.0	35.2
30–39	342	23.8	27.3	59	7.6	18.7	239	23.4	28.8
>39	177	12.3	16.2	60	7.7	16.3	620	60.6	16.3
Marital status									
Married	445	30.9	36.2	132	16.9	29.1	604	59.0	30.3
Unmarried	994	69.1	63.8	647	83.1	70.9	419	41.0	69.7
Education									
Low	271	18.8	16.3	162	20.8	17.9	198	19.4	15.3
Middle	927	64.4	65.6	472	60.6	62.1	583	57.3	65.3
High	241	16.7	18.1	145	18.6	20.0	237	23.3	19.4
Military career									
Rank									
Enlisted	524	36.4	24.8	208	26.7	33.1			
Non-commissioned officer	767	53.3	62.1	497	63.8	55.7			
Commissioned officer	148	10.3	13.1	74	9.5	11.3			
Unit									
Combat	674	46.8	23.8	166	21.3	23.3			
Medical	61	4.2	5.9	55	7.1	8.0			
Combat support	704	48.9	70.3	558	71.6	68.7			

%w = weighted percentage.

*Weights were used to assure: (1) representativeness of the deployed sample for the reference population taking into account oversampling of combat units, eligibility and response according to rank, unit and location; (2) comparability of the deployed with the never deployed sample according to rank, unit, operational area, gender, age, educational level, number of years spent at school and having children; and (3) comparability of the general population sample with both military samples with regard to age, sex and marital status (individuals who were not employed were excluded from the general population sample).

Statistical analysis

We used weighting procedures to achieve: (a) the representativeness of the DS sample for the reference population ($N = 9617$), (b) the comparability of the NS with the DS sample and (c) the civilian sample with the DS sample. The weighting procedure is described in detail in the online supplementary material.

For the comparison of both military samples with the civilian sample, logistic, multinomial logistic and linear regressions were applied for binary, multicategorical and dimensional outcomes, respectively. For counted outcomes (i.e. the number of reported symptoms), negative binomial regressions were applied. Comparisons between DS and the civilian sample were always conducted for the total DS sample as well as separately for DS with low and high combat exposure since there is evidence that DS with high combat exposure have a higher risk for mental disorders (Iversen *et al.* 2008; Jacobson *et al.* 2008). Since differences in demographic characteristics between the three comparison groups could not be neutralised completely (see Table 1), we conducted a sensitivity analysis where we re-analysed differences between groups adjusting for age and marital status. All regressions used the robust Huber–White sandwich estimator for statistical inference in weighted data (Royall, 1986). Associations were quantified with odds ratios (OR) for logistic and multinomial logistic and with incidence rate ratios (IRR) for negative binomial regressions. Statistical significance was assessed at the 5% level (two-sided tests). All analyses were conducted with Stata 12.1. (Stata Corp, 2012).

Results

Prevalence of 12-month mental disorders

The prevalence of any 12-month mental disorder was lower in NS (14.4%) compared with civilians (20.0%; OR: 0.7, 95% CI: 0.5–0.99) but was not significantly different in DS (16.6%). Compared with civilians, NS had a lower probability of meeting criteria for alcohol (OR: 0.2, 95% CI: 0.1–0.6) and nicotine dependence (OR: 0.5, 95% CI: 0.3–0.7) but there were no differences regarding the prevalence of internalising disorders. DS had a lower prevalence of any other anxiety disorder (OCD, GAD) (OR: 0.4, 95% CI: 0.2–0.6), alcohol (OR: 0.3, 95% CI: 0.1–0.6) and nicotine dependence (OR: 0.5, 95% CI: 0.3–0.6) compared with civilians. The prevalence of all other specific diagnoses did not differ significantly between the military samples and civilians (Table 2). When differences between DS and civilians were analysed separately for DS with low and high combat exposure, DS with high combat exposure had a higher prevalence of panic/agoraphobia (OR: 2.7, 95% CI: 1.4–5.3) and PTSD (OR: 3.2, 95% CI: 1.3–8.0), while DS without combat exposure had a lower prevalence of any mood disorder (OR: 0.5, 95% CI: 0.4–0.8) compared with civilians. All other patterns of results were similar for DS with low and high combat exposure (Table S1). A sensitivity analysis adjusting for age and marital status showed the same differences between the three groups and estimates of associations were almost identical (data available on request).

Severity of 12-month mental disorders

We analysed differences between military samples and civilians regarding comorbidity, self-rated impairment (for internalising disorders) and number of reported symptoms (for SUD) as measures of disorder severity (Table 3). For internalising disorders, logistic regressions revealed higher proportions of severe cases of anxiety disorders compared with civilians only among NS (OR: 5.4, 95% CI: 1.7–17.5). For SUD, the number of reported symptoms in individuals with ND was lower in both military samples (DS: IRR: 0.8, 95% CI: 0.7–0.8; NS: IRR: 0.7, 95% CI: 0.6–0.7) and it was also lower in individuals with AUD in the DS sample (IRR: 0.7, 95% CI: 0.6–0.9) compared with civilians. DS with low and high combat exposure showed a similar pattern of results compared with civilians regarding the severity of mental disorders except that DS with low combat exposure had a lower proportion of moderate cases of anxiety disorders compared with civilians (OR: 0.3, 95% CI: 0.1–0.9) which was not found for DS with high combat exposure (Table S2). Adjusting for age and marital status did not affect these results.

Discussion

This study compared military personnel with and without a history of deployment and sociodemographically comparable civilians regarding the prevalence and severity of 12-month DSM-IV mental disorders. The study is among the few that have been able to conduct a standardised comparison of military and civilian samples across the same timeframe using identical assessment methods. We found rather similar rates for internalising disorders and lower rates for SUD in both military samples compared with civilians. The same pattern was observed for measures of disorder severity where we found a lower severity of SUD and a comparable severity of most internalising disorders. Elevated rates among military personnel compared with civilians were only found for DS with high combat exposure and this was restricted to panic/agoraphobia and PTSD.

These findings differ from the US and the UK comparisons which found overall higher rates of mental disorders in military personnel compared with civilians (Kessler *et al.* 2014*b*; Goodwin *et al.* 2015). Findings also differ from previous UK data suggesting higher rates of alcohol misuse in the military compared with the general population, although this study only stratified by gender and age (Fear *et al.* 2007). There are several possible reasons for these divergent findings.

First, there are noteworthy differences in design and methods employed in this study compared with those reported by Kessler *et al.* (2014*b*) and Goodwin *et al.* (2015). Military samples in these studies were representative of the serving military. The DS sample, which was used as reference for the calibration of both NS and civilians was only representative of two ISAF contingents. Selection mechanisms that led to the assignment to these contingents might have led to different prevalences of mental disorders than would have been observed in the entire serving military. Moreover, the UK study used a self-report instrument (General Health Questionnaire) and the US study used a self-administered version of the CIDI as well as the Posttraumatic stress disorder Checklist for the assessment of mental disorders instead of structured interviews that were employed in this study. However, this is unlikely to explain any cross-study differences since military and civilian samples were always assessed with the same instruments so potential bias would apply to both populations.

Second, there are differences in deployment characteristics and the military structure between

Table 2. *Twelve-month prevalence of DSM-IV mental disorders in DS, NS and civilians*

	Military samples			Differences	
	Deployed ($n = 1439$) % (95% CI)	Never deployed ($n = 779$) % (95% CI)	Civilians ($n = 1023$) % (95% CI)	Deployed *v.* civilians OR (95% CI)	Never deployed *v.* civilians OR (95% CI)
Any disorder[a]	16.6 (14.6–18.9)	14.4 (11–18.7)	20.0 (16.4–24.3)	0.8 (0.6–1.1)	0.7 (0.5–0.99)
No. of diagnoses[a]					
0	83.4 (81.1–85.4)	85.6 (81.3–89.0)	80.0 (75.7–83.6)	1.0	1.0
1	8.1 (6.7–9.7)	7.7 (5.1–11.6)	10.7 (8.0–14.1)	0.7 (0.5–1.1)	0.7 (0.4–1.2)
2	5.6 (4.4–7.1)	4.7 (3.1–7.2)	6.8 (4.6–9.9)	0.8 (0.5–1.3)	0.6 (0.4–1.2)
3	1.8 (1.2–2.7)	0.9 (0.3–2.1)	1.1 (0.5–2.2)	1.6 (0.7–3.8)	0.8 (0.2–2.4)
4	1.2 (0.7–2.0)	1.1 (0.4–2.5)	1.5 (0.7–3.2)	0.8 (0.3–2.0)	0.7 (0.2–2.1)
Internalising disorders					
Anxiety disorders					
Panic/agoraphobia	5.3 (4.2–6.7)	1.8 (0.9–3.4)	3.1 (1.7–5.5)	1.7 (0.9–3.3)	0.6 (0.2–1.4)
PTSD	2.8 (2.0–4.0)	1.2 (0.5–2.6)	1.4 (0.6–3.3)	2.0 (0.8–4.9)	0.8 (0.3–2.6)
Phobias	5.7 (4.5–7.1)	6.2 (4.3–9.0)	6.5 (4.5–9.4)	0.9 (0.5–1.4)	0.9 (0.5–1.7)
Other anxiety disorders	1.9 (1.2–2.8)	2.8 (1.3–5.8)	5.1 (3.4–7.6)	0.4 (0.2–0.6)	0.5 (0.2–1.3)
Any anxiety disorder	12.1 (10.3–14.1)	9.8 (7.1–13.5)	12.7 (9.8–16.3)	0.9 (0.7–1.3)	0.8 (0.5–1.2)
Mood disorders					
Major depressive disorder	3.4 (2.5–4.6)	2.2 (1.1–4.1)	4.2 (2.6–6.5)	0.8 (0.5–1.4)	0.5 (0.2–1.1)
Bipolar disorder	1 (0.6–1.8)	1.5 (0.4–5.0)	1.2 (0.5–3.0)	0.9 (0.3–2.5)	1.2 (0.3–5.9)
Any mood disorder	4.4 (3.4–5.8)	3.7 (2.0–6.8)	5.4 (3.6–8.0)	0.8 (0.5–1.4)	0.7 (0.3–1.5)
Substance use disorders					
Alcohol abuse	3.3 (2.5–4.5)	2.3 (1.3–3.9)	4.0 (2.4–6.8)	0.8 (0.4–1.5)	0.6 (0.3–1.2)
Alcohol dependence	1.4 (0.9–2.3)	1.1 (0.5–2.6)	4.6 (2.9–7.2)	0.3 (0.1–0.6)	0.2 (0.1–0.6)
Any alcohol use disorder	3.4 (2.6–4.6)	2.3 (1.3–4.0)	7.6 (5.3–10.8)	0.4 (0.3–0.7)	0.3 (0.1–0.6)
Nicotine dependence	10.7 (9.0–12.6)	11.4 (8.4–15.3)	20.9 (17–25.4)	0.5 (0.3–0.6)	0.5 (0.3–0.7)

Phobias: Social phobia, specific phobia; other anxiety disorders: GAD, OCD.

[a]Without nicotine dependence.

Weights were used to assure: (1) representativeness of the deployed sample for the reference population taking into account oversampling of combat units, eligibility and response according to rank, unit and location; (2) comparability of the deployed with the never deployed sample according to rank, unit, operational area, gender, age, educational level, number of years spent at school and having children; and (3) comparability of the general population sample with both military samples with regard to age and marital status (individuals who were not employed were excluded from the general population sample).

Germany, UK and the USA in terms of tour length, preparation and involvement in combat events (Wittchen *et al.* 2012*b*; Trautmann *et al.* 2013; Zimmermann *et al.* 2014) which might result in an overall lower degree of exposure to stressful experiences in German deployed personnel. This might explain why we found no elevated rates of mental disorders in deployed personnel compared with civilians. However, an overall effect of deployment on mental health only exists for the US but not for the UK military (Sundin *et al.* 2014) suggesting that these deployment characteristics might only explain the differences between the present study and the study of Kessler *et al.* (2014*b*) which included a high proportion of previously deployed personnel. Moreover, the US and UK military might differ from the German forces in terms of recruitment, career mechanisms, regulations and the availability and accessibility of supportive resources including mental health services. In particular, the lower rates of SUD in the German military compared with civilians might be the result of strict regulations regarding substance use (at least for alcohol use) and earlier treatment seeking compared with civilians, probably mediated by disciplinary measures in case of substance-related offenses and the corrective influence of the military unit (Zimmermann *et al.* 2012). Alternatively, differences in cultures between militaries with regard to substance use might also be relevant.

Third, both Kessler *et al.* (2014*b*) and Goodwin *et al.* (2015) argue that predisposing vulnerability factors for

Table 3. *Severity of 12-month DSM-IV mental disorders in recently DS, NS and civilians*

	Internalising disorders		Substance use disorders	
	Anxiety disorder % (95% CI)	Mood disorder % (95% CI)	AUD Mean (S.D.)	ND Mean (S.D.)
Recently deployed				
Impairment				
Mild	48.1 (38.5–57.9)	25.7 (15–40.3)		
Moderate	42.9 (33.6–52.8)	56.6 (42.0–70.0)		
Severe	9.0 (4.7–16.5)	17.8 (9.6–30.5)		
No. of symptoms			4.4 (2.1)[a]	4.0 (1.4)[a]
Never deployed				
Impairment				
Mild	35.0 (19.8–54.0)	14.9 (3.1–49.1)		
Moderate	44.0 (27.1–62.4)	40.8 (16.2–71.1)		
Severe	21.0 (9.6–40.0)[a]	44.4 (18.1–74.1)		
No. of symptoms			5.8 (2.1)	3.5 (0.9)[a]
Civilians				
Impairment				
Mild	47.4 (31.5–63.8)	28.4 (13.1–50.9)		
Moderate	48.0 (31.8–64.5)	36.6 (19.1–58.5)		
Severe	4.7 (2.2–9.4)	35.1 (17.2–58.4)		
No. of symptoms			5.9 (3.3)	5.2 (1.4)

Anxiety disorder: any panic disorder, agoraphobia, posttraumatic stress disorder, social phobia, specific phobia, generalised anxiety disorder, obsessive compulsive disorder; mood disorders: any major depressive disorder, dysthymia; AUD, alcohol use disorder; ND, nicotine dependence.

[a]Significant difference compared with civilians ($p < 0.05$).

the development of mental disorders (e.g. parental psychopathology (Knappe *et al.* 2009), early adverse experiences (Kessler *et al.* 1997)) might be more common in military personnel compared with civilians which could be the result of self-selection processes (Kessler *et al.* 2014*b*; Goodwin *et al.* 2015). If this was the case, our findings would suggest that this self-selection of vulnerable individuals into military service might exist to a lesser extent in the German military or that military selection and attrition processes might counteract these effects.

Finally, divergent findings compared with previous studies might be the result of cross-national differences in occupational cultures in general. Nations vary considerably in occupational factors such as working conditions, occupational health and safety systems as well as prevention and compensation approaches to work-related health problems, which might be related to the prevalence of mental disorders in the working population (World Health Organization, 2012). Another specific occupational aspect might be an over-reporting of mental health symptoms in studies which have been specifically designed to target an individual occupational group such as military personnel (Goodwin *et al.* 2013, 2015). In addition to putative effects of assessment procedures, which can impact on this response bias (self-report questionnaire *v.* structured interviews), one might speculate that German military personnel are less likely to endorse sensitive private information such as mental health symptoms than US and UK military personnel. This could be explained by perceived roles, stigmatisation or suspected disadvantages related to disclosure of mental disorder which could differ between the German military and other forces. In summary, there are several putative reasons for differences in military-civilian comparison between the present German study and recent US and UK findings, which might be fruitful targets for future research.

Beyond differences to previous US and UK comparisons we observed two more specific findings that might have implications for service provision and intervention. First, elevated rates of mental disorders among DS compared with civilians were only found for PTSD and panic/agoraphobia. This is in line with research showing particularly strong relations between traumatic event exposure and these mental disorders (Ayazi *et al.* 2014) which should be considered when screening for deployment-related mental health problems. Second, we found more severe

cases of anxiety disorders in the NS sample compared with civilians. This might reflect a reduced recognition and treatment allocation of at least some anxiety disorders in the population of NS which warrants further investigation.

This study has some limitations. The DS sample was representative for two contingents of DS and does not represent the entire deployed population in the German forces. However, we have no evidence that these contingents differ considerably from others. In addition, we cannot rule out the possibility of an underreporting, especially for SUD. However, this would only mask differences between soldiers and the general population if this occurred to a higher extent in soldiers. Besides, previous studies have shown that the used interview and its confidential administration allow a valid estimation of prevalence rates for SUD (Kessler *et al.* 1998; Lachner *et al.* 1998). We were also not able to assess females in this study because of the low number in the German military. Finally, interpretations regarding differences between military personnel and civilians have still to be done with caution since even a careful calibration of samples cannot consider all putatively relevant variables.

Conclusion

The findings of this study suggest that rates and severity of mental disorders are similar or even lower in the German military compared with sociodemographically matched civilians, irrespective of deployment. The concentration of available resources on an improved identification and care for high-risk subgroups, particularly among deployed personnel with high combat exposure, might therefore be the most appropriate strategy. Differences to comparisons from the USA and the UK, which observed higher rates of mental disorders in the military, might be explained by differences in study methods, deployment characteristics, military structures, self-selection processes and mental health in the working population. The findings of this study might apply to other nations (e.g. Netherlands, Australia) which report prevalence rates of mental disorders that are similar to those in the German military (Hodson *et al.* 2011; Reijnen *et al.* 2015). Whilst the suggested methodological explanations for divergent findings should be considered in the conduct and interpretation of future studies, differences in recruitment strategies, selection processes and disclosure of mental disorder might be promising targets for further investigation of these mechanisms and the role they may have in determining military mental health.

Supplementary material

The supplementary material for this article can be found at http://dx.doi.org/10.1017/S204579601600024X.

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Conflict of Interest

HUW is member of advisory boards and received grant support and travel compensation by Servier, Lundbeck, Novartis, Pfizer and Sanofi which could be perceived as a potential conflict of interest. PZ is employed by the German Armed Forces. His employment had no influence on the study design; the collection, analysis and interpretation of data. All other authors declare that they have no conflict of interests.

Ethical Standard

The study was approved by the TUD Ethics Board (EK 72022010), after internal Bundeswehr approval, and was performed according to ICH-GCP (Good Clinical Practice) Guidelines.

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4 Susceptibility to others' emotions as moderator of immediate self-reported and biological stress responses to witnessing trauma

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Susceptibility to others' emotions moderates immediate self-reported and biological stress responses to witnessing trauma

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ABSTRACT

Background: The peri-traumatic stress response is a strong predictor of symptom development after trauma exposure. Regarding witnessing trauma, the stress response might depend on the susceptibility to others' emotions (emotional contagion, EC). This study investigated whether EC moderates the immediate stress response using a trauma film paradigm.

Methods: Ninety-five healthy participants were randomly exposed to a trauma or a neutral film. Perceived stressfulness of the film and pre-to post-film changes in self-reported anxiety, heart rate and saliva cortisol levels were assessed. EC towards negative and positive emotions was measured using the emotional contagion scale and its emotion-specific subscales.

Results: Overall, the trauma film was perceived as distressing and elicited an increase in self-reported anxiety, heart rate and saliva cortisol levels relative to the neutral film. EC towards negative emotions was positively related to the perceived stressfulness of the film, increased anxiety and increased heart rate. The association with saliva cortisol levels was also in the expected direction, but not statistically significant. These associations were not found for EC towards positive emotions.

Discussion: EC towards negative emotions may be an important predictor of trauma exposure outcomes. Further research should clarify its specific contribution in witnessing and undergoing trauma.

1. Introduction

Traumatic events have a high lifetime prevalence ranging between 60.7% and 76.2% across different countries (Benjet et al., 2015). Exposure to traumatic events is associated with a higher risk for various mental disorders such as posttraumatic stress disorder (Karam et al., 2014; McLaughlin et al., 2015), anxiety disorders (Asselmann, Wittchen, Lieb, Perkonigg, & Beesdo-Baum, 2017), depressive disorders (Suliman et al., 2009) and substance use disorders (Fetzner, McMillan, Sareen, & Asmundson, 2011), but also for somatic morbidity and decreased quality of life (Mölsä et al., 2014; Nicol et al., 2016). However, the majority of trauma-exposed individuals do not develop any disorder (Breslau, 2009; Wittchen et al., 2012). Therefore, knowledge about factors associated with the probability of developing trauma-related psychopathology is of vital importance for the development of targeted interventions.

Since the third revision of the Diagnostic and Statistical Manual of Mental Disorders, the definition of traumatic events explicitly includes not only events that are personally experienced but also events that are witnessed (DSM−III−R, American Psychiatric Association, 1987). These events include witnessing someone being seriously hurt, seeing atrocities or witnessing dead bodies. Witnessing traumatic events are among the most frequent traumatic experiences (Benjet et al., 2015) and are of high current relevance in the context of natural disasters, terrorist attacks and military crises (Holman, Garfin, & Silver, 2014; Monfort & Afzali, 2017; Weems et al., 2007; Wittchen et al., 2012).

The reasons why individuals can develop psychopathological reactions to events that are actually experienced by others has become an important focus of social and neurobiological sciences (Hein & Singer, 2008; Patki, Salvi, Liu, & Salim, 2015). An important mechanism in the

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link between witnessing traumatic events and adverse mental health consequences is the ability to share affective experiences of others. This ability is based on shared neural networks for first-hand and observed emotional experiences through activation in neural structures that are also active during direct experience (Singer & Lamm, 2009; Wild, Erb, & Bartels, 2001; Zaki, Wager, Singer, Keysers, & Gazzola, 2016). As a result, witnessing and personally experiencing an adverse event can elicit similar patterns of emotional (e.g. distress, anxiety, sadness) and biological (e.g. elevated heart rate, increased cortisol levels) (Chou, La Marca, Steptoe, & Brewin, 2014; Holz, Lass-Hennemann, Streb, Pfaltz, & Michael, 2014; Weidmann, Conradi, Gröger, Fehm, & Fydrich, 2009) responses which are in turn robustly associated with the development of mental disorders such as PTSD (de Quervain, Aerni, Schelling, & Roozendaal, 2009; McFarlane, Barton, Yehuda, & Wittert, 2011; Ozer, Best, Lipsey, & Weiss, 2003).

A crucial process associated with the ability to share affective experiences is the multifaceted construct of empathy. While empathy is usually described as a capacity with positive consequences for social interaction, prosocial behavior and mental health outcomes, it may also confer risk for personal distress, depression and anxiety when witnessing the suffering of other persons (Tone & Tully, 2014). The latter is the case when self-other distinction is impaired, e.g. because of individual predispositions or as a consequence of strong negative emotions (Kanske, Böckler, Trautwein, Parianen Lesemann, & Singer, 2016; Klimecki & Singer, 2012). A crucial construct in this context is the susceptibility to others' emotions, also called emotional contagion (EC). EC has been defined as the tendency to automatically mimic the expressions, postures and behaviors of others, and thereby to feel a reflection of others' emotions generated by afferent feedback (Hatfield, Rapson, & Le, 2011). The result is an emotional and physiological state matching between a target and an observer (de Waal & Preston, 2017). EC and empathy are proposed to be distinct but partially overlapping constructs (de Vignemont & Singer, 2006; Luckhurst, Hatfield, & Gelvin-Smith, 2017; Stavrova & Meckel, 2017). In particular, EC can be seen as a precursor of empathy, which does not involve self-other distinction (Klimecki & Singer, 2013). Thus, EC might be a valuable construct for the explanation of personal distress after witnessing suffering in others as described above. Importantly, EC is conceptualized as a stable trait (Lundqvist, 2006; Rueff-Lopes & Caetano, 2012) that is supposed to vary between individuals as a result of genetics, early experiences and personality (Doherty, 1997). This variability has been shown for EC towards emotions in general but also for EC towards emotions with either negative or positive valence (Lundqvist, 2006, 2008). Especially EC towards negative affect is associated with harm avoidance (Lundqvist, 2008), emotional fragility (Coco, Ingoglia, & Lundqvist, 2014), trait anxiety and neuroticism (Doherty, 1997), which in turn are also related to autonomic and endocrine activity (Hauner et al., 2008; Kao et al., 2016; Xin et al., 2017). Although it seems likely that variability in EC also influences the emotional and biological response to witnessed traumatic events, we are not aware of studies that have empirically tested this association.

This study aimed at investigating whether EC moderates the self-reported and biological stress response to a witnessed traumatic event in young, healthy individuals within a randomized controlled analogue design. Specifically, we used the trauma film paradigm (TFP), in which non-clinical participants watch films containing scenes, which depict stressful or traumatic events (Holmes & Bourne, 2008). The TFP has been shown to reliably elicit strong stress responses in self-reported and biological stress measures such as increased anxiety, heart rate and saliva cortisol (James et al., 2016). The used film scene can be seen as a model of witnessed traumatic events because it shows a women being raped and hurt. We hypothesized that with increasing EC, the perceived stressfulness of the film as well as the immediate stress reaction (state anxiety, heart rate, saliva cortisol) would increase in those subjects watching a trauma film relative to a non-emotional control condition (neutral film). Since previous research suggests associations between EC and emotional processing for EC towards negative emotions rather than for EC towards emotions in general, we expected a moderation of stress reactivity for EC towards negative emotions (fear, sadness, anger) but not for EC towards positive emotions.

2. Methods

2.1. Participants

The study population was defined as healthy individuals aged between 18 and 40 years. Participants were recruited in a university environment through advertisements and social media. To prevent negative long-term consequences of watching a trauma film, we applied the following exclusion criteria: history of sexual or violence trauma exposure (including experiences of close relatives), history of psychotic symptoms or substance use disorder, and current mood or anxiety disorder. We also excluded subjects with a current somatic disease (e.g. adrenocortical dysfunction) or medication (e.g. corticosteroids) that could interfere with the biological stress measures, as well as subjects being familiar with the used film material. Of 353 screened individuals, 101 subjects could be included in the study. Among individuals which had to be excluded, 53.6% screened positive for a current mental and 14.3% for a current alcohol use disorder, 16.7% reported current illegal drug use, 21.8% had a history of violent trauma, 5.2% had a current somatic disease or medication and 7.5% were familiar with the study film material. Five individuals did not respond to the invitation. Ninety-six volunteers finally agreed to participate and were randomized to either one of the film conditions while assuring equal group size (n = 48). During the study, one participant in the trauma film condition refused further participation resulting in a final trauma film condition group size of n = 47. Demographic and baseline sample characteristics are shown in Table 1. The mean age of participants was 23.7 years (SD = 3.9) with a roughly equal gender distribution (54.7% females). There were no differences between participants in the trauma and the

Table 1
Demographic and baseline sample characteristics.

	Trauma film		Neutral film		Trauma vs Neutral		
					χ^2/t value	df	p
Demographics							
Female, n (%)	26	55.3	26	54.2	0.01	1	0.910
Age, mean (SD)	24.5	4.2	22.9	3.4	−2.09	93	0.040
Baseline characteristics							
Lifetime traumatic events, mean (SD)	2.0	1.6	2.3	2.1	0.87	93	0.384
Trait anxiety, mean (SD)	36.6	9.0	35.6	8.4	−0.53	93	0.596
Self-reported anxiety, mean (SD)	34.9	6.9	32.2	9.2	−1.63	93	0.107
Heart rate[a], mean (SD)	76.0	11.9	74.8	12.9	−0.43	86	0.665
Saliva cortisol, mean (SD)	9.9	6.2	9.5	5.6	−0.34	93	0.734
Emotional contagion							
Negative, mean (SD)	7.6	1.8	7.4	1.6	−0.80	93	0.425
Positive, (SD)	8.3	1.5	7.9	1.9	−1.12	93	0.267

Lifetime traumatic events: Trauma History Questionnaire, trait anxiety: trait version of the State Trait Anxiety Inventory, self-reported anxiety: state version of the State Trait Anxiety Inventory, emotional contagion: Emotional Contagion Scale and its subscales.
T tests were conducted for dimensional and chi square tests for binary outcomes.
[a] Mean value of a 3-min baseline interval.

neutral film condition regarding demographic and baseline characteristics except that participants in the trauma film condition were slightly older (difference: 1.6 years, t (93) = -2.1 p = .040) (Table 1).

2.2. Measures

2.2.1. In– and exclusion criteria

History of trauma exposure was assessed using the Trauma History Questionnaire (THQ, Hooper, Stockton, Krupnick, & Green, 2011). The THQ consists of 24 questions on a range of traumatic events that can be answered with yes or no. The THQ has good reliability and validity in clinical and non-clinical samples (Hooper et al., 2011). To screen for current (past 12 months) and past mental disorders, we used the screening scale of the Munich Comprehensive International Diagnostic Interview, which has been widely used in epidemiological and clinical studies (Wittchen & Perkonigg, 1997). Current somatic diseases and medication that could interfere with the study measures were assessed according to a standardized protocol according to previous studies (e.g. Trautmann et al., 2018).

2.2.2. Emotional contagion

We used the Emotional Contagion Scale (ECS, Doherty, 1997) to measure EC. The ECS is a 15-item scale, which aims to measure 'individual differences in susceptibility to catching the emotions of other individuals' (Doherty, 1997). Each item describes a specific emotional expression of another person and a congruent emotional reaction from a first-person perspective (e.g. 'If someone I'm talking with begins to cry, I get teary-eyed.') to which individuals respond on a 4-point scale (from 'never true' to 'always true'). The ECS correlates positively with interpersonal reactivity (which covers the aspects personal distress, empathic concern and perspective taking) but can be discriminated from general perceived distress (Rueff-Lopes & Caetano, 2012). The ECS has a hierarchical structure with 5 subscales (representing EC towards different emotions: fear, sadness, anger, happiness and love), which can be allocated to two higher order factors: ES towards negative (fear, sadness, anger) and towards positive affect (happiness and love) (Lundqvist, 2008). The ECS total score and the two higher order subscores show good consistency and reliability (Doherty, 1997; Rueff-Lopes & Caetano, 2012) while the consistency of the emotion-specific subscales is partially low ($\alpha < 0.70$) (Lundqvist & Kevrekidis, 2008). Although our sample was much smaller compared to these validation samples, we found the same pattern of higher consistency for the ECS total score and the two higher order subscores (α between 0.68 and 0.75) compared to the five emotion-specific subscores (α between 0.49 and 0.64). Thus, we used the two higher order subscales to test our hypotheses that EC, particularly to negative emotions, moderates the immediate stress response to the film material. Although we had no hypothesis regarding EC towards the five specific emotions, we also report the findings for these emotion-specific subscales in the supplementary material as exploratory analyses.

2.2.3. Perceived stressfulness of the film

Following the presentation of the film scene, participants rated how distressing they experienced the film on a visual analogue scale ranging from 0 (not at all) to 100 (extremely).

2.2.4. Trait and state anxiety

As peri-traumatic anxiety seems to be among the most important distress symptoms in the prediction of symptoms occurring after watching trauma film material (Hagenaars, Brewin, van Minnen, Holmes, & Hoogduin, 2010), we assessed change in self-reported state anxiety in response to the films using the state subscale of the State Trait Anxiety Inventory (STAI-S, Spielberger, 1983). The STAI-S consists of 20 items that are rated on a 4-point Likert scale and has excellent psychometric properties (Spielberger, 1983). The 20-item trait component of the STAI (STAI-T) was also used as a control measure (see data analysis).

Table 2
Pairwise correlations of baseline sample characteristics and emotional contagion.

		(1)	(2)	(3)	(4)	(5)	(6)	(7)
Baseline characteristics								
(1)	Lifetime traumatic events	1						
(2)	Trait anxiety	-.03	1					
(3)	Emotion dysregulation	.15	.71***	1				
(4)	Self-reported state anxiety	-.10	.40***	.30**	1			
(5)	Heart rate[a]	.12	-.01	-.06	.08	1		
(6)	Saliva cortisol	.12	.09	.06	.21*	.23*	1	
Emotional contagion [b]								
(7)	Negative affect	-.07	.27**	.21*	.22*	.09	.13	1
(8)	Positive affect	-.09	-.26**	-.28**	-.17	.15	.19	.33**

*p < .01, **p < .01,***p < .001.
[a] Mean value of a 3-min baseline interval.
[b] Emotional contagion scale (ECS) scores.

2.2.5. Emotion dysregulation

As control measure, emotion dysregulation was measured using the 36-item Difficulties in Emotion Regulation Scale (DERS, Gratz & Roemer, 2004). This instrument has a five-point response format and comprises difficulties in the regulation of emotions regarding six dimensions (non-acceptance, goal-directed behavior, impulsivity, awareness, use of strategies and clarity). The DERS has high internal consistency, good test–retest reliability, and adequate construct and predictive validity (Gratz & Roemer, 2004) and has already been associated with symptom development after exposure to traumatic stress (Tull, Barrett, McMillan, & Roemer, 2007).

2.2.6. Heart rate

Heart rate was assessed as a marker for the autonomic stress reactivity to the film. Electrocardiogram (ECG) was measured continuously during the 15 min of the film sequence and in a 3-min interval directly before the film (baseline interval) using an Eindhoven Lead II setup with two standard Ag/AgCL electrodes (8 mm; Marquette Hellige, Freiburg, Germany). The ECG signal was filtered online with an 8–13 Hz bandpass filter, amplified with the factor 2000, and sampled at a rate of 100 Hz using a Coulbourn V75-04 bioamplifier (Allentown, PA). Then, the ECG signal was visually inspected and artifact-corrected using ANSLAB (Blechert, Peyk, Liedlgruber, & Wilhelm, 2016). ECG R-R intervals (converted to beats per minute) were reduced into half-second bins and averaged across blocks of 10 s. For the subsequent analyses, the 10-s blocks were collapsed into means of a baseline interval (3 min before the film), an immediate film reaction (first minute) and three further blocks ending after 5, 10 and 15 min of the film. ECG was not available for 5 individuals in the neutral film condition and 2 individuals in the trauma film condition due to technical difficulties.

2.2.7. Saliva cortisol

We assessed salivary cortisol levels as a marker of the endocrine stress reactivity since it is thought to play a vital role in the etiology of trauma-related symptoms (de Quervain et al., 2009; McFarlane et al., 2011; Ozer et al., 2003). Saliva samples were collected immediately before the film as well as 1, 10, 20 and 30 min after the film using Salivettes 'code blue' devices (Sarstedt, Germany). Samples were stored at −20 °C in a laboratory freezer until analyses. After thawing, saliva samples were centrifuged for 10 min at 4000 rpm. Salivary cortisol levels were determined by using a commercially available luminescence assay (LIA, IBL-Hamburg, Germany).

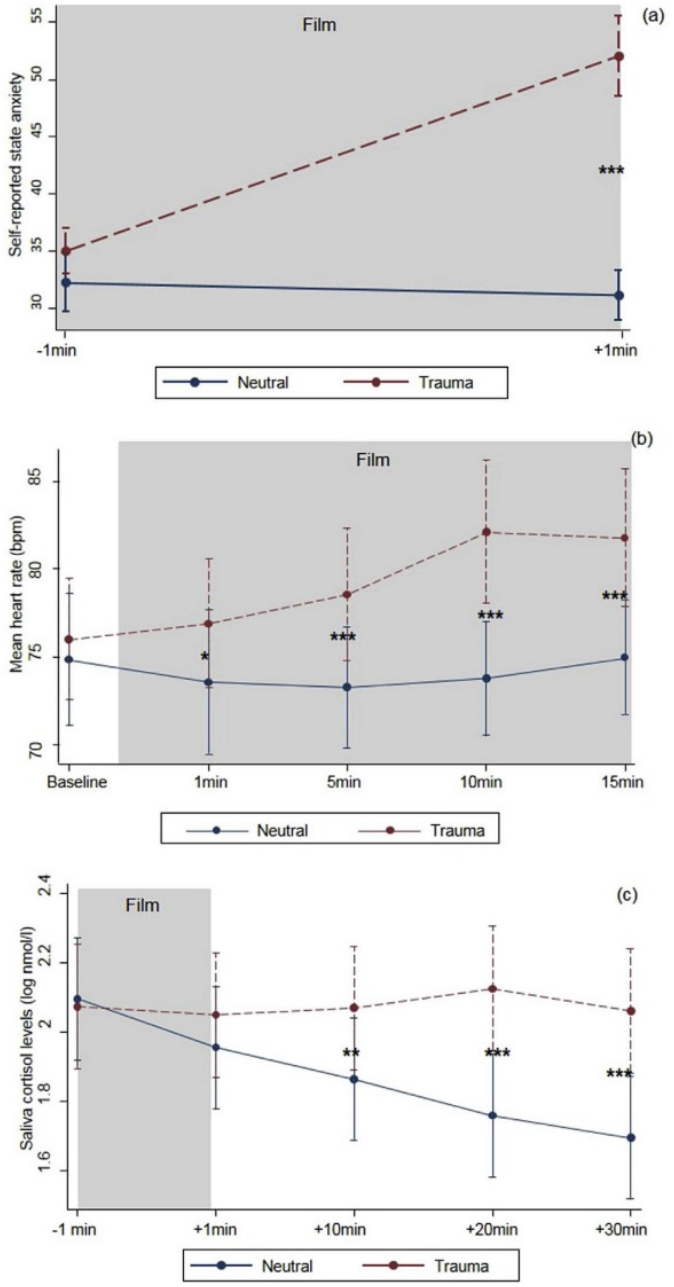

Fig. 1. Effects of the trauma film on self-reported anxiety, heart rate and saliva cortisol levels.
Results from mixed effects regressions including a two-way interaction film condition x time with first time point as reference. Self-reported anxiety: state version of the Trait State Anxiety Inventory, Mean heart rates: dots represent the mean value of the interval to the preceding time point except for baseline which is the mean of a 3-min interval before the film; * < 0 .05, **p < .01. ***p < .001.

2.3. Film material

The chosen trauma scene from the movie 'Irreversible' (Feldner, Zvolensky, Eifert, & Spira, 2003) by Gaspar Noé is widely used in TFPs and was shown to elicit a strong immediate stress response (self-reported distress, heart rate) as well as short-term trauma-related symptoms (i.e. intrusions) in both male and female participants (Arnaudova & Hagenaars, 2017; Weidmann et al., 2009). The 15-min scene shows a young woman leaving a party and being assaulted on her way home, brutally raped and beaten up by a man. As it is recommended to control for the potentially arousing effects of watching a film when using the trauma film paradigm (Arnaudova & Hagenaars, 2017), we chose a control condition showing an emotionally neutral film where a young woman gives systematic instructions on how to build a garden house. This film was comparable to the trauma film in terms of an equal length and having a female person as the main actor.

2.4. Procedure

All participants were instructed to refrain from smoking, eating and drinking anything but water 60 min prior to the assessment to avoid confounding of biological stress measures. First, participants completed STAI-S, STAI-T and ECS after providing informed consent. Then, they were led into the laboratory room and sat before a 22″ computer screen, 80 cm away from the monitor, and ECG electrodes were attached. After a 3-min interval during which baseline heart rate was measured while participants were looking at a neutral screensaver, the first saliva sample was taken, room lights were switched off and participants watched a 15-min neutral or trauma film sequence according to their randomized condition. Heart rate was continuously measured during the film. After the film, participants in both conditions completed the STAI-S and saliva cortisol levels were repeatedly measured. At the end of the study, participants received either a compensation of 10 Euros or credit points if they were psychology students (20% of the sample). All participants were assessed between 1p.m. and 8p.m. to reduce variability in cortisol measures due to circadian rhythms (Debono et al., 2009). The entire study procedure was approved by the Ethics Board of the Technische Universität Dresden (EK 23022008).

2.5. Data analysis

A skew-normal linear regression (Azzalini & Capitanio, 1999) was used to test whether saliva cortisol levels were considerably skewed. Since this was the case (α = 9.2 [8.7–9.7] p < .001), saliva cortisol levels were first log transformed to reduce skewness. To test for differences between participants of the trauma and the neutral film condition in demographics and baseline characteristics T Tests and Chi Square Tests for dimensional and categorical outcomes, respectively, were conducted. We further checked for associations between ECS scores and baseline variables by computing a pairwise correlation matrix.

To test for differences in the perceived stressfulness of the film between groups, linear regression analyses were conducted. For all other indicators of the immediate stress response (self-reported anxiety, heart rate, saliva cortisol), mixed effects regressions with random intercept parameter were fitted. This means that for each individual observation, scores on the dependent variable are predicted by the intercept that varies across groups (Garson, 2012). The use of a mixed effects model with random intercept parameter addresses regression to the mean, which could otherwise yield biased results (Oberg & Mahoney, 2007). We fitted models that added the main effect term and a two-way interaction term film condition (between subject) x time (within subject) with the first time point (baseline) as reference. To analyze the moderating role of EC, the above-mentioned analyses were repeated with adding the three-way interaction terms film condition x time x ECS scores to the models. Models were fitted separately for EC towards negative and towards positive emotions while consistent findings across both dimensions were taken as evidence for general rather than emotion-specific effects of EC. All models were adjusted for age and gender. We also tested whether results would change when additionally adjusting for the number of previous traumatic event experiences, trait anxiety and emotion dysregulation because those factors were previously demonstrated to be potential confounders of immediate stress reactions (de Veld, Riksen-Walraven, & de Weerth, 2012; James et al., 2016; Kudielka, Hellhammer, & Wüst, 2009).

To assure that the sample size provides sufficient statistical power to

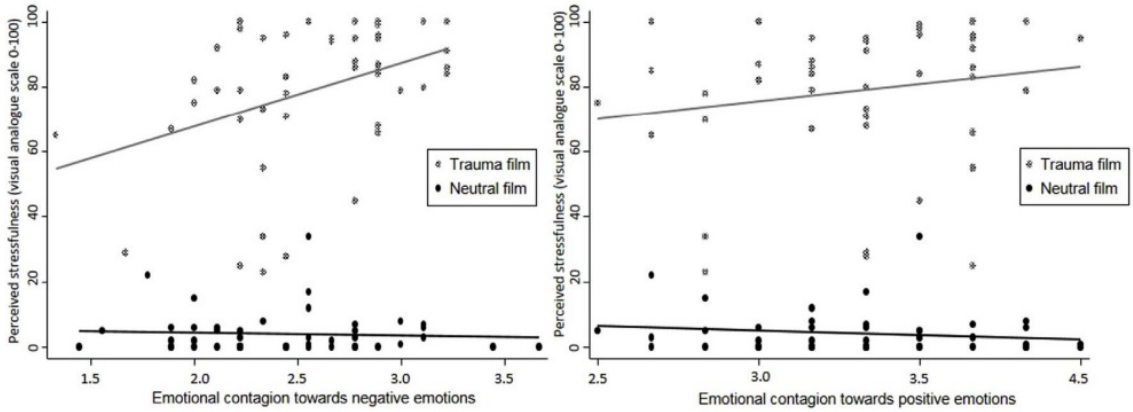

Fig. 2. Perceived stressfulness (visual analogue scale 0–100) of the film by levels of emotional contagion towards negative and positive emotions.
Results from linear regressions including a two-way interaction term film condition x emotional contagion adjusted for sex, age, history of traumatic events, trait anxiety and emotion dysregulation. The two-way interaction film condition x emotional contagion towards negative emotions is statistically significant (p = .005).

be able to detect effects even for three-way analyses, we ran several power analyses using the procedure SIMPOWER. Given our sample size and data distributions, a simulation of F tests with 1000 replications assuming a 5% significance level as well as 8 groups for the subjective, 20 groups for the heart rate and 24 groups for the cortisol measures (group x time x EC) revealed a statistical power of > .99.

Results are reported as beta values with 95% confidence intervals. Statistical significance was evaluated at the two-sided 5% level. In graphical illustrations of results, the procedure MARGINS was used to calculate predicted probabilities and EC was categorized into tertiles (low, moderate, high). All analyses were conducted with Stata 14.1 (Stata Corp., 2015).

3. Results

3.1. Baseline measures and emotional contagion

EC towards negative and positive emotions were (in opposite directions) correlated with trait anxiety (negative: r = 0.27, p = .007, positive: r = −0.26, p = .010) and emotion dysregulation (negative: r = 0.21 p = .043, positive: r = −0.28, p = .005). EC towards negative emotions was also correlated with state anxiety at baseline (r = 0.22 p = .030). (Table 2). All other correlations between EC and baseline measures were not significant (p > .05).

3.2. Stress response to the film

Participants in the trauma film condition rated the film as more distressing (M = 78.7, SD = 21.9) than participants in the neutral film condition (M = 4.0, SD = 6.6, difference: b = 74.7 [67.8–81.3] p < .001). Relative to the neutral film condition, the trauma film condition was associated with an increase in self-reported state anxiety (b = 18.3 [14.7–21.9] p < .001) and an increase in heart rate for 1 min (b = 2.2 [0.1–4.3] p = .042), 5 min (b = 4.1 [2.0–6.3] p < .001), 10 min (b = 7.2 [5.0–9.3] p < .001) and 15 min (b = 5.7 [3.5–7.8] p < .001) of the film. The trauma film condition was also associated with higher increase in saliva cortisol levels 10 min (b = 0.2 [0.1–04] p = .001), 20 min (b = 0.4 [0.3–0.5] p < .001) and 30 min (b = 0.4 [0.3–0.5] p < .001) after the films (Fig. 1a–c) compared to the neutral film condition. The differences between experimental conditions did not change after additionally adjusting for the number of lifetime traumatic events, trait anxiety and emotion dysregulation.

3.3. Moderation of the stress response to the film by EC

In the trauma film condition, the distress rating of the film increased with increasing EC towards negative emotions (b = 18.1 [7.1–29.2] p = .002). This association was not found in the neutral film condition (b = −2.0 [-11.8-7.9] p = .689) with a significant film condition x EC towards negative emotion interaction (b = 20.1 [6.0–34.2] p = .006). EC towards positive emotions was not related to the distress rating of the film in any of the film conditions (ps > .150) (Fig. 2).

Increase in self-reported state anxiety from pre to post film was positively associated with EC towards negative emotions in the trauma film (b = 6.4 [0.5–12.2] p = .034) but not in the neutral film condition (b = 0.1 [-5.2-5.4] p = .971), although this difference did not reach statistical significance (b = 6.3 [-1.7-14.2] p = .122). EC towards positive emotions was not related to pre to post film changes in state anxiety in any of the film conditions (ps > .463) (Fig. 3).

Increase in heart rate compared to baseline was positively related to EC towards negative emotions in the trauma film condition for measures 5 min (b = 4.7 [1.4–8.1] p = .006), 10 min (b = 6.8 [3.5–10.2] p < .001) and 15 min (b = 3.5 [0.2–6.8] p = .040) of the film (Fig. 3). These associations were not found in the neutral film condition with significant three-way interactions film condition x time x EC towards negative emotions for measures 5 min (b = 5.6 [1.1–10.2] p = .015) and 10 min (b = 7.3 [7.8–11.8] p = .002) of the film. EC towards positive emotions was not related to increase in heart rate in any of the film conditions (ps > .173).

Increase in saliva cortisol levels compared to baseline was related to EC towards negative emotions in the expected direction, but not statistically significant, in the trauma film condition 30 min after the film (b = 0.2 [-0.02-0.5] p = .074) (Fig. 3). EC towards negative emotions was also negatively related to cortisol levels in the neutral film condition 20 min after the film (b = −0.3 [-0.5-(-0.1)] p = .010). There were no associations between EC towards positive emotions and increase in saliva cortisol in any of the film conditions (p > .198).

There were no main effects of EC scores on any measure of stress reactivity to the trauma film (p > .101). All results regarding the moderating role of EC remained stable after additionally adjusting for the number of lifetime traumatic events, trait anxiety and emotion dysregulation.

Exploratory analyses on the association between the five emotion-specific subscales and the stress response to both film conditions are shown in the supplemental material.

4. Discussion

This analogue study investigated whether EC moderates the immediate stress response to a witnessed trauma in healthy individuals. We used the trauma film paradigm within a randomized controlled design. Our main finding was that the stress reaction to a witnessed

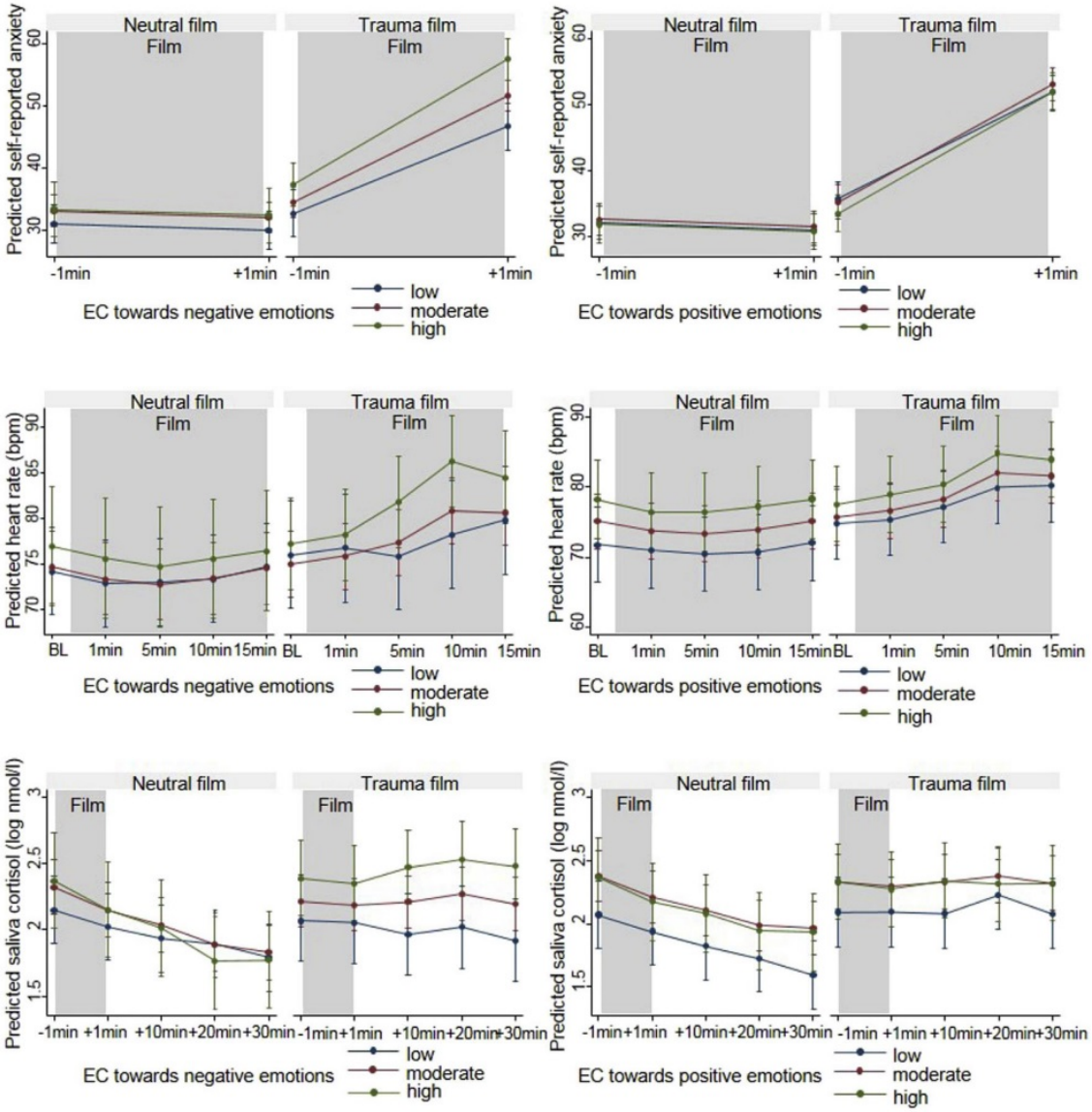

Fig. 3. Effects of the trauma film on self-reported anxiety, heart rate and saliva cortisol levels by levels of emotional contagion towards negative (left column) and positive (right column) emotions

Results from mixed effects regressions with first time point as reference adjusted for sex, age, history of traumatic events, trait anxiety and emotion dysregulation. In the trauma film condition, significant time x emotional contagion towards negative emotions were found for self-reported state anxiety (b = 6.4 [0.5–12.2] p = .034), for heart rate for measures 5 min (b = 4.7 [1.4–8.1] p = .006), 10 min (b = 6.8 [3.5–10.2] p < .001) and 15 min (b = 3.5 [0.2–6.8] p = .040) of the film, and for saliva cortisol levels 30 min after the film by trend (b = 0.2 [-0.02-0.5] p = .074)

For graphical illustration, levels of emotional contagion are shown in three categories (low, moderate, high)

BL = Baseline; Self-reported anxiety: state version of the Trait State Anxiety Inventory, Mean heart rates: dots represent the mean value of the interval to the preceding time point except for baseline which is the mean of a 3-min interval before the film.

trauma increased with higher values of EC towards negative emotions in those individuals witnessing the trauma film relative to individuals in the neutral film condition.

We could not find an association between EC towards positive emotions and any of the examined stress reactivity measures. This finding provides further evidence that EC is not a unidimensional construct (Lundqvist & Kevrekidis, 2008), and that only EC towards negative emotions could represent a valuable target for a vulnerability factor for adverse outcomes following exposure to potentially traumatic events. From a methodological point of view, these findings suggest that the total score of the ECS scale might not be a useful measure in the context of emotional and biological responsivity. It is further noteworthy that the perceived stressfulness of the film as well as all investigated measures of the stress response to the trauma film (state anxiety, heart rate, saliva cortisol) increased with higher levels of EC towards negative emotions except for post-film changes in cortisol for which only a trend for an association was observed. It should be noted that participants in the trauma film condition showed only a modest increase in cortisol levels after the film, which can be explained by a marked anticipatory anxiety causing a ceiling effect in the cortisol reactivity. This ceiling effect could have led to an underestimation of the moderating role of EC in the trauma film condition.

Although these findings were broadly in line with our hypothesis, the mechanisms underlying the found associations have still to be determined. One could argue that EC towards negative emotions just represents a general emotional lability, especially since it has been associated with harm avoidance (Lundqvist, 2008), emotional fragility (Coco et al., 2014), trait anxiety and neuroticism (Doherty, 1997).

However, we were able to show that the associations between EC towards negative emotions and stress reactivity remained stable after adjusting for trait anxiety and emotion dysregulation, which suggest that the associations are at least partly independent of the effects of other possible determinants of emotional reactivity. Since EC is also related to other forms of empathy (Luckhurst et al., 2017), it remains unclear whether the found associations are just a function of empathy rather than a specific effect of EC. Although this question remains open for future investigation, one could speculate that EC as an automatic process (Hatfield et al., 2011) might have a more direct effect on emotional reactivity than empathy which is likely to be modulated by self-other distinction (Klimecki & Singer, 2012). Instead of findings being attributable to empathy rather than EC, it seems more likely that EC and empathy could have additive or interactive effects on stress reactivity, which clearly warrants further investigation.

This study has several limitations. First, EC was not randomized or manipulated in this study, so associations may not be interpreted as causal inference. Second, the sample size did not allow for potentially relevant subgroup analyses (e.g. gender, familiarity with the suffering target (Langford et al., 2006)) or investigations of bimodal associations. Moreover, the limited sample size resulted in broad confidence intervals for the estimated effects, which is why point estimates of effect quantifications should be interpreted with caution. Third, we can only speculate about specific peri-traumatic processes involved (e.g. attentional processes) since the participants' behavior during the film was not closely monitored. Fourth, we excluded individuals with mental disorders and several somatic diseases, resulting in a healthy and resilient sample. Thus, the generalizability of the presented findings to the general population or at-risk samples might be limited.

4.1. Conclusions and future directions

Considering these limitations, our findings suggest EC towards negative emotions as a promising novel target for research on the development of adverse consequences after witnessing traumatic events. It could be a particularly relevant construct for analogue studies, which are often based on witnessing others being harmed, but also for research on collective witnessing events such terror attacks and natural catastrophes. It might also help to explain the phenomenon of "secondary traumatization" were close relatives of traumatized individuals exhibit emotional and behavioral problems (Yager, Gerszberg, & Dohrenwend, 2016). Future studies should directly investigate the association between EC and symptom development after witnessing trauma. This could be done by replicating this study including repeated measures of affect, arousal or intrusions in the aftermath of watching a trauma film, e.g. through diary or ecological momentary assessment (James et al., 2016; Kleim, Graham, Bryant, & Ehlers, 2013). It seems also warranted to investigate how EC relates to different forms of empathy and how these constructs affect reactions to distressing events. Future studies may consider top-down cognitive empathic processes, which could moderate the association between EC and stress reactivity (de Waal & Preston, 2017). Moreover, within-subject designs have advantages regarding confounding variables, which should be considered in future studies. Additional measures of trait emotionality as well as peri-traumatic processes such as attention or direct behavioral fear measures such as freezing (Hagenaars, Roelofs, & Stins, 2014; Laposa & Rector, 2012; Verwoerd, Wessel, & de Jong, 2012) could further facilitate a better understanding of mechanisms underlying the observed associations. Future studies might also benefit from the inclusion of film material with other valences (e.g. positive material) to provide a better control of arousal (Arnaudova & Hagenaars, 2017). Given the potentially limited external validity of analogue studies (Ehring, Kleim, & Ehlers, 2011; James et al., 2016), observational longitudinal studies should also investigate the relationships between EC, real potentially traumatic events and symptom development. Another question worth investigating is whether EC towards negative emotions is specifically related to the response to witnessing trauma or to potentially traumatic experiences in general as suggested by the association between EC and trait anxiety (as found in this study) and neuroticism (Doherty, 1997). Further knowledge on these aspects could clarify whether EC towards negative emotions constitutes a promising target for the development of interventions to prevent adverse consequences following trauma exposure. For now, our findings suggest that the susceptibility to negative emotions of others' is an important moderator of emotional and physical responses after witnessing an analogue trauma, with increased responses in those with higher susceptibility.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.brat.2018.09.001.

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5 Stress-induced alcohol craving after psychological trauma: the role of childhood trauma and stress reactivity

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ORIGINAL INVESTIGATION

The role of childhood trauma and stress reactivity for increased alcohol craving after induced psychological trauma: an experimental analogue study

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Abstract

Background Traumatic events are associated with alcohol use problems with increased alcohol craving as a potential mediator. There is still a lack of knowledge regarding the causal nature of this association and its underlying mechanisms. This study investigated the effects of acute trauma exposure on alcohol craving in healthy individuals considering the role of stress reactivity and childhood trauma (CT) using a laboratory randomized controlled design.

Methods Ninety-five healthy participants were randomly exposed to a trauma or a neutral film. History of CT, and pre- to post-film changes in craving (craving reactivity, CR), anxiety, skin conductance, heart rate, and saliva cortisol levels were assessed. Moreover, associations between trauma film exposure and CR, the moderating role of CT, and associations between CT, stress reactivity, and trauma-induced CR were analyzed.

Results Relative to the neutral film, the trauma film elicited an increase in CR in females but not in males. In males but not in females, the association between trauma film exposure and CR was moderated by CT, with trauma-induced CR increasing with the number of CT. In males, CT was related to decreased cortisol reactivity and increased heart rate and skin conductance response of which skin conductance was also associated with CR.

Discussion These findings provide further evidence for a causal link between traumatic experiences and CR. While this association seems to be stronger in females, males might still be at risk in case of other vulnerability factors such as CT, with altered sympathetic stress reactivity as a potential contributing mechanism.

Keywords Trauma · Stress · Cortisol · Heart rate · Anxiety · Analogue study · Trauma film paradigm

Introduction

Per definition, traumatic events include exposures to death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence (American Psychiatric Association 2013). In the general population, about two out of three individuals report to have experienced at least one traumatic event (Benjet et al. 2015). Various studies have found strong associations between traumatic events and the initiation and escalation of alcohol use and the development of alcohol use disorders (Stewart 1996; Hasin et al. 2007; Debell et al. 2014). These conditions are associated with high individual and societal burden (Rehm et al. 2009), both directly and indirectly via the aggravation of other trauma-related disorders (McCarthy and Petrakis 2010; Carter et al. 2011). However, there is still a lack of knowledge regarding (1) the causal nature of the association between trauma exposure and alcohol use and (2) the underlying processes involved.

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Most evidence for the association between traumatic events and problematic forms of alcohol use stems from observational studies showing higher rates of alcohol use, heavy alcohol use, and alcohol-associated disorders in trauma-exposed individuals (Hooper et al. 2008; Watt et al. 2012; Kachadourian et al. 2014). However, controlled experimental studies in humans, which are needed to investigate the causal effect of trauma exposure on alcohol use, are scarce. For one reason, valid laboratory methods to measure alcohol use after experimental manipulation of an independent variable (e.g., trauma exposure) are limited (see Jones et al. 2015 for recent developments). A suitable alternative to measure alcohol use in experimental settings is to assess alcohol craving, i.e., the desire to consume alcohol. Alcohol craving is related to a higher motivation to seek for and engage in alcohol consumption, detectable e.g. through increased attention towards alcohol-related cues (Franken 2003, 2007). Since there is also some evidence that the association between trauma exposure and alcohol use is mediated by alcohol craving (Gruesser et al. 2007; Tripp et al. 2015), it represents a valuable target to study potential acute effects of traumatic events on alcohol use in experimental studies.

Some studies already found increases in alcohol craving after exposure to or imagery of trauma-related cues in alcohol use disorder patients with a history of traumatic events (Coffey et al. 2006, 2010; Kwako et al. 2015; Ralevski et al. 2016). However, studies in clinical samples do not allow any conclusions about the potential role of trauma exposure in the development of problematic alcohol use since stress reactivity and craving are altered in dependent individuals (Muehlhan et al. in press; Robinson and Berridge 2008). Existing evidence from non-clinical samples is limited to non-traumatic stressors showing increases in attention towards alcohol cues and craving after stress induction in both regular and heavy drinkers (Nesic and Duka 2008; Field and Quigley 2009). We are unaware of experimental studies investigating the association between trauma exposure and craving in non-clinical samples despite the fact that laboratory traumatic stressors are available and widely used to study the biological and psychological consequences of trauma exposure (Holmes and Bourne 2008; James et al. 2016).

Although the self-medication of trauma-related adverse psychological states by alcohol intake is a well-established and empirically supported model (Khantzian 1997; Leeies et al. 2010; Crum et al. 2013), several findings suggest controversies (Stevens et al. 2008; Fetzner et al. 2011; Trautmann et al. 2017). Recent theoretical models, mainly based on animal models, have suggested that stress reactivity might be a key component in the relationship between traumatic events and excessive alcohol use (Edwards et al. 2013; Lijffijt et al. 2014). The increased availability of central norepinephrine following acute stress impairs prefrontal control functions (Schwabe and Wolf 2011; Allen et al. 2014), stimulates a shift from goal-directed to habitual behavior (Möschl et al. 2017; Otto et al. 2013; Wirz et al. 2018), and biases processing of motivational information (Ehlers and Todd 2017). Moreover, the glucocorticoid increase following stress facilitates dopaminergic activity within the mesolimbic reward system (Koob 2009; Spanagel et al. 2014). Thus, stress may enhance the anticipated rewarding effect of alcohol and, in turn, further increase the motivation to drink (Becker 2017). Despite this strong theoretical foundation, experimental human studies investigating the associations between trauma exposure, stress reactivity, and craving are still lacking.

Despite the epidemiological evidence for a relationship between traumatic events and measures of alcohol use described earlier, several studies did not confirm this association (North et al. 2011; Trautmann et al. 2015, 2016). These heterogeneous results suggest existing moderating factors that have to be considered when investigating the mechanisms linking trauma exposure and alcohol use. The experience of traumatic events during childhood might be such a moderating factor since it was demonstrated to be associated with an increased risk of alcohol use problems after trauma exposure during later life (Clarke-Walper et al. 2014; Keyes et al. 2014; Schäfer et al. 2017). Childhood trauma is also related to changes of physiological and subjective stress reactivity under conditions of acute stress (Heim et al. 2000; Bunea et al. 2017) and to alterations in stress-induced craving (Elton et al. 2015; Potthast et al. 2015). Thus, it seems crucial to consider childhood traumas when studying associations between acute trauma exposure, craving, and stress reactivity.

The aim of this study was to investigate the effects of acute trauma exposure on alcohol craving in healthy individuals if considering the potential moderating roles of stress reactivity and childhood traumas. We conducted a laboratory randomized controlled study using the trauma film paradigm as a laboratory trauma analogue stressor (James et al. 2016). We hypothesized that (a) acute trauma exposure would lead to an increase in reported alcohol craving compared to a neutral condition, (b) trauma-related increase in craving would be positively related to experienced childhood traumas, and (c) the association between childhood traumas and trauma-induced craving could be explained by increased peritraumatic stress reactivity, indicated by (c1) an association between childhood traumas and stress reactivity and (c2) an association between stress reactivity and craving. Since considerable sex differences exist in psychological and physiological reactions to traumatic stress (with an overall higher vulnerability for females) (Hagborg et al. 2017), we tested these hypotheses separately for males and females. As exploratory analyses, we additionally investigated the association between acute trauma exposure and increased attention towards alcohol-related cues.

Methods

Participants

Participants were recruited in a university environment through advertisements and social media. Individuals had to meet the following inclusion criteria: (1) being between 18 and 40 years old, range of age was limited to reduce age-related variance in stress reactivity and recall bias of childhood traumas (Green et al. 2010; Strahler et al. 2010); (2) drinking alcoholic beverages at least occasionally (once per month in the past year) since it is unlikely that alcohol craving would be relevant in abstinent individuals. Since the study included exposure to a very stressful stimulus as well as stress reactivity measures, we applied several exclusion criteria to prevent sustained adverse psychological consequences as well as confounding of the study measures. Individuals were initially screened according a standardized protocol (e.g., Trautmann et al. 2017) and excluded if they reported a history of lifetime sexual or violent trauma exposure and a history of lifetime psychotic symptoms or substance use disorder or current mood or anxiety disorders. We also excluded subjects with a current somatic disease (e.g., adrenocortical dysfunction) or medication (e.g., corticosteroids) that could interfere with the biological stress measures. Overall, we screened 353 individuals: 101 of them were eligible for participation. Fifty-five individuals were excluded due to past sexual or violent trauma exposure (65.5% females). Finally, 96 subjects agreed to participate and were randomized to either the trauma or a neutral condition (also see description of the trauma film paradigm subsequently) with an equal group size ($n = 48$). One participant in the trauma condition dropped out during the study resulting in a group size of $n = 47$ for this condition. The mean age of the sample was 23.7 years (SD = 3.9) with 54.7% being female. Childhood traumas were experienced by 63.2% of the sample with males being more likely to be exposed to crime victimization compared to women ($\chi^2(1) = 5.7$, $p = .017$). There was no sex difference regarding the number of childhood traumas but males were more likely to be exposed to crime victimization compared to women ($\chi^2(1) = 5.7$, $p = .017$). Participants in the trauma and the neutral film condition did not differ in demographic characteristics, reported childhood traumas and stress parameters at baseline except that participants in the trauma film condition were slightly older (Table 1).

The trauma film paradigm

We used the trauma film paradigm (TFP) as a laboratory trauma-analogue stressor. In the TFP, non-clinical participants watch films containing scenes showing traumatic events such as accidents, physical assault, or rape (Holmes and Bourne 2008). The TFP has been shown to reliably elicit strong stress responses and psychological symptoms such as intrusions, which are also observed in the aftermath of actual traumatic events (James et al. 2016). As the trauma film, we used a 15-min scene from the movie "Irreversible" (France, 2003) by Gaspar Noé showing a young woman leaving a party and being assaulted on her way home, brutally raped and beaten up by a man. This scene is a well-validated traumatic stressor, which elicits strong, self-reported, autonomic, and endocrine stress responses as well as short-term trauma-related symptoms (i.e., intrusions) in both male and female participants (Trautmann et al. in press; Weidmann et al. 2009; Arnaudova and Hagenaars 2017). Following recent recommendations to control for the potentially arousing effects of watching a film when using the TFP (Arnaudova and Hagenaars 2017), we chose a control condition showing an emotionally neutral film of an equal length where a young woman gives systematic instructions on how to build a garden house.

Measures

Alcohol craving

We used the short form of the revised version of the Alcohol Craving Questionnaire (ACQ-SF-R, Singleton et al. 1994; German version: Raabe et al. 2005), a 12-item self-report measure using a 7-point Likert response format. The ACQ-R has high internal consistency ($\alpha = .94$ in this sample), test–retest reliability, and convergent validity (Raabe et al. 2005).

Childhood trauma

Childhood traumas were assessed using the Trauma History Questionnaire (THQ, Hooper et al. 2011; German version: Maercker 2002). Other than the broader construct of childhood maltreatment, which has been the predominant construct in previous studies on effects of early adversities, the THQ measures the history of exposure to actual traumatic events according to the DSM-IV A1 criterion of posttraumatic stress disorder (American Psychiatric Association 2000). The THQ consists of questions on 24 traumatic events including information about the age of trauma exposure. All reported traumatic events experienced until the age of 18 were summarized. The THQ has proven reliability and validity in different clinical and non-clinical samples (Hooper et al. 2011).

Stress reactivity

Changes in state anxiety during the experimental conditions were assessed using the state subscale of the State Trait Anxiety Inventory (STAI-S, Spielberger 1983). The STAI-S consists of 20 items that are rated on a 4-point Likert scale and has good psychometric properties (Spielberger 1983) ($\alpha = .89$ in this sample).

Table 1 Demographic and baseline sample characteristics

	Trauma film		Neutral film		Trauma vs. neutral		
					χ^2/F value	df	p
Demographics							
Female, n (%)	26	(55.3)	26	(54.2)	0.01	1	0.910
Age, mean (SD)	24.5	(4.2)	22.9	(3.4)	4.09	93	0.043
Baseline characteristics							
Trait anxiety, mean (SD)	36.6	(9.0)	35.6	(8.4)	0.08	93	0.776
Emotional contagion, mean (SD)	8.3	(1.5)	7.9	(1.9)	2.06	93	0.155
AUDIT-score, mean (SD)	7.2	(4.3)	7.0	(3.9)	0.03	93	0.859
Number of childhood traumas, mean (SD)							
0	18	(38.3)	17	(35.4)			
1–2	21	(44.7)	21	(43.8)			
> 2	8	(17.0)	10	(20.8)	0.24	2	0.887
Type of childhood traumas, n (%)							
Crime victim	8	(17.0)	7	(14.6)	0.11	1	0.745
Accident	10	(21.3)	11	(22.9)	0.04	1	0.847
Natural catastrophe	8	(17.0)	10	(20.8)	0.22	1	0.635
Life-threatening illness	12	(25.5)	17	(35.4)	1.09	1	0.296
Other	7	(14.9)	7	(14.6)	0.01	1	0.966
Age at first childhood trauma, mean (SD)	10.7	(4.8)	12.4	(3.8)	2.40	58	0.127
State anxiety, mean (SD)	34.9	(6.9)	32.2	(9.2)	3.24	93	0.075
Skin conductance level[1], mean (SD)	4.0	(0.4)	4.4	(0.4)	0.26	89	0.611
Heart rate[1], mean (SD)	76.0	(11.9)	74.8	(12.9)	0.86	86	0.356
Saliva cortisol, mean (SD)	9.9	(6.2)	9.5	(5.6)	0.16	93	0.694

[1] Mean value of a 3-min baseline interval

F tests from robust regression models for dimensional and chi-square tests for categorical outcomes are reported

To investigate the autonomic stress reactivity, we assessed skin conductance and heart rate activity changes in response to the film. Electrodermal activity (EDA) and electrocardiogram (ECG) were recorded continuously during the 15 min of the film sequence and in a 3-min interval directly before the film (baseline interval) by using, for each measurement, two standard Ag/AgCl electrodes (8 mm; Marquette Hellige, Freiburg, Germany) that were placed on the hypothenar muscle of the palmar surface of a participant's non-dominant hand and in an Eindhoven Lead II setup, respectively. The SC was recorded by a Coulbourn S71-22 skin conductance coupler that provided a constant 0.5 V across the two electrodes filled with isotonic 0.5 M sodium chloride electrode gel and was sampled with a rate of 10 Hz. The ECG signal was filtered online with an 8- to 13-Hz bandpass filter, amplified with the factor 2000, and sampled at a rate of 100 Hz using a Coulbourn V75-04 bioamplifier (Allentown, PA). Then, the ECG signal was visually inspected and artifact-corrected using ANSLAB (Blechert, Peyk, Liedlgruber, and Wilhelm 2016). Skin conductance level and ECG R-R intervals (converted to beats per minute) were reduced into half-second bins and averaged across blocks of 10 s. Following a previous study (Trautmann et al. in press), the 10-s blocks were collapsed into means of a baseline interval (3 min before the film), an immediate film reaction (first minute), and three further blocks ending after 5, 10, and 15 min of the film to reduce variability. Since we were only interested in autonomic reactivity to the experimental condition (stress vs. neutral), peak-to-baseline changes were calculated for heart rate (heart rate reactivity, HRR) and skin conductance (skin conductance reactivity, SCR) by subtracting the mean value of the baseline interval from the largest mean value of the four intervals during the film (i.e., peak-to-baseline change). Due to technical problems, HRR and SCR measures were not available for seven and five individuals, respectively.

As a marker of endocrine stress reactivity, we assessed salivary cortisol levels. Saliva samples were collected 1 min before the film as well as 1, 10, 20, and 30 min after the film using Salivettes "code blue" devices (Sarstedt, Germany). Participants were instructed to gently chew swabs until soaked with saliva. Samples were stored at − 20 °C in a laboratory freezer until analyses. After thawing, saliva samples were centrifuged for 10 min at 4000 rpm. Salivary cortisol levels were determined by using a commercially available luminescence assay (LIA, RE62019 IBL-Hamburg, Germany). To reduce variability in cortisol measures due to circadian rhythms

(Debono et al. 2009), all saliva samples were taken between 1 p.m. and 8 p.m. We calculated the area under the curve with respect to increase (AUCi) (Pruessner et al. 2003) as a measure of cortisol reactivity (CortR).

Attention towards alcohol-related cues

Following previous studies (e.g., Field and Quigley 2009), we used a visual probe paradigm to measure increased attention towards alcohol-related cues (i.e., attentional bias). The material comprised 14 pairs of pictures, with one alcoholic and one matched non-alcoholic beverages in each pair. Six non-alcoholic picture pairs were used as practice stimuli. The task began with 10 practice trials before two buffer trials, in which neutral pairs were again presented. Those were followed by 112 critical trials, in which alcohol–non-alcohol picture pairs were presented. In each trial, a fixation cross was presented for 500 ms, followed by the presentation of a picture pair for 500 ms, with one picture on the left of the screen and one on the right. After picture offset, an arrow that pointed up or down (visual probe stimulus) was presented on either the left or right of the screen. Participants were required to identify the probe by pressing the Q (down) or the P (up) button on the keyboard. Appearances of each picture (left or right) and probe (up or down) were counterbalanced and probes replaced alcoholic and non-alcoholic pictures with equal frequency. The visual probe task was programmed in Presentation software. Attention towards alcohol-related cues was calculated by subtracting mean reaction times to probes that replaced alcohol pictures from mean reaction times to probes that replaced non-alcohol pictures (Field and Quigley 2009).

Control measures

As a measure of current problematic alcohol use, we used the Alcohol Use Disorder Identification Test (AUDIT, Saunders et al. 1993; German version: Rumpf et al. 2002). The AUDIT is a reliable (α = .77 in this sample) and valid measure of harmful drinking (Conigrave et al. 1995b). The AUDIT score ranges from 0 to 40 while scores of 8 or above are an indicator of harmful drinking (Conigrave et al. 1995a).

Drinking motives were assessed since drinking to cope was shown to increase the association between stress and alcohol-related measures (Field and Quigley 2009). Drinking motives were evaluated using the revised drinking motives questionnaire (DMQ-R, Cooper 1994; German version: Kuntsche et al. 2006), a reliable (α = .85 in this sample) and valid 20-item questionnaire of which we used the subscale assessing coping motives as a control measure.

We further assessed trait anxiety with the trait subscale of the State Trait Anxiety Inventory (STAI-T, Spielberger 1983). Trait anxiety is likely to confound associations between early environmental factors (e.g., childhood traumas) and reactions to later stressors (Allwood et al. 2011; Villada et al. 2016).

Recent findings indicate that the stress reaction to a laboratory trauma stressor depends on the general susceptibility to others' emotions (i.e., emotional contagion) (Trautmann et al. in press) because participants react to emotions that are experienced by the protagonists of the traumatic film material. Thus, we also included the emotional contagion scale (ECS) (Doherty 1997; German version: Falkenberg 2005), a 15-item questionnaire which showed acceptable reliability in this sample (Cronbach's α = .78) as a control measure (see data analysis).

Procedure

The entire study procedure took place at the Faculty of Psychology at the Technische Universität Dresden. All participants were instructed to refrain from smoking, eating, and drinking anything but water 60 min prior to the assessment to avoid confounding of biological stress measures. First, participants were informed that they will potentially watch a stressful film scene and were asked to provide informed consent. Afterwards, they completed a series of self-report measures (STAI-S, STAI-T, DMQ-R, AUDIT, and ECS). After completing a craving baseline measure (ACQ-SF-R), participants were led individually into the laboratory room and sat before a 22-in. computer screen, 80 cm away from the monitor, and ECG/EDA electrodes were attached. After a 3-min interval during which baseline heart rate and skin conductance were measured while participants were looking at a neutral screensaver, the first saliva sample was taken, room lights were switched off, and participants watched a 15-min neutral or trauma film sequence. Heart rate and skin conductance were continuously measured during the film. After the film, participants completed the visual probe task. Participants in both conditions then completed a further assessment of state anxiety and craving, and saliva cortisol levels were repeatedly measured. At the end of the study, participants received contact information for psychological support in case of negative emotional reactions and received either a compensation of 10 Euros or credit points if they were psychology students (20% of the sample). The entire study procedure was approved by the Ethics Board of the Technische Universität Dresden (EK 23022008).

Data analysis

To test for differences between participants of the trauma and the neutral film condition in demographics and baseline variables, F tests from robust regression models (see following text) for dimensional and chi-square tests for categorical outcomes are reported.

To test our hypothesis, we fitted different regression models: We tested for potential effects of experimental

condition (trauma vs. neutral) on craving reactivity (post-film craving adjusted for baseline values) (hypothesis a); for a potential interaction effect between number of childhood traumas (reported in the THQ) and experimental condition on craving reactivity (hypothesis b); for a potential interaction effect between number of childhood traumas (reported in the THQ) and experimental condition on stress reactivity during the task (SCR, HRR, CortR) (hypothesis c1); and, finally, for a potential association between stress reactivity and craving reactivity (hypothesis c2). We additionally tested the association between acute trauma exposure and increased attention towards alcohol-related cues as exploratory analysis.

As in most psychological and physiological studies, assumptions of the conventional general linear model (ANOVA, linear regression) including normally distributed residuals with equal variances were violated in our data (residual distributions were checked graphically), which can result in poor power and inaccurate confidence intervals and effect sizes (Field and Wilcox 2017). Following the current recommendations, we therefore used robust regression models (Field and Wilcox 2017). Robust regressions drop the assumptions of the general linear model by using a robust sandwich estimation of standard errors and by down-weighting the observations with large residuals and omission of outlying residuals (Royall 1986). To provide a meaningful supplement to null hypothesis testing and to facilitate the interpretation of our results, we additionally applied Bayesian linear regressions for our main hypotheses (Baldwin and Larson 2017). As we were interested in how much evidence is available in our data that is in line with our hypotheses, we used the procedure BAYES with flat priors (i.e., the case that no prior information on the data distribution is available) based on Markov chain Monte Carlo (MCMC) sampling followed by the procedure BAYESTEST to test, for instance, how much evidence is in the data for group differences or associations greater than 0.

Since sex can moderate psychological and physiological reactions to traumatic stress (with an overall higher vulnerability for females) (Hagborg et al. 2017), we also tested for potential interaction effects between sex and all independent variables (film condition, number of childhood traumas, stress reactivity). This was also done for harmful drinking status since differences in alcohol use are likely to affect stress reactivity and craving (Spanagel et al. 2014). We also carefully selected control variables that could modulate craving and stress reactivity after stress exposure (e.g., Field and Quigley 2009; Trautmann et al. in press). Therefore, all models including craving reactivity as a dependent variable were adjusted for current problematic alcohol use (AUDIT score) (not in models including interaction with harmful drinking) and coping drinking motives. Also, all models including measures of stress reactivity as a dependent variable were adjusted for current problematic alcohol use, trait anxiety, and susceptibility to others' emotions (ECS score). We also tested whether potential sex differences in stress reactivity were attributable to intake of oral contraceptives. In graphical illustrations of results, the procedure MARGINS was used to calculate probabilities predicted by the respective model. Moreover, the number of childhood traumas was categorized into 0, 1–2, and more than 2 experiences for illustrative purposes. The raw data underlying these figures as well as the effects of covariates in the regression models are provided in the supplemental material. All analyses were conducted with Stata 15.1 (Stata Corp., 2017).

Results

Stress reactivity to the trauma film paradigm

The trauma film paradigm elicited a stress response in both self-reported and physiological measures. Increase in state anxiety was higher in the trauma compared to that in the neutral film group ($b = 18.5$ [14.9–22.1], $p < 0.001$). This was also the case for HRR ($b = 5.1$ [2.8–7.3], $p < 0.001$) and SCR ($b = 0.4$ [0.01–0.8], $p = 0.045$) as well as for CortR (AUCi) ($b = 63.2$ [16.2–110.3], $p = 0.009$). There were no group × sex interactions on stress reactivity except for state anxiety: females showed stronger increases than males in the trauma film compared to the neutral film condition (interaction: $b = 9.2$ [2.4–15.9], $p = 0.008$). Group × sex interactions on stress reactivity did not change after adjusting for intake of oral contraceptives. We also observed no significant group × harmful drinking interactions (p's > .097).

Trauma film and craving reactivity

In the total sample, we found an effect of the trauma condition on craving reactivity. Individuals who watched the trauma film reported higher craving reactivity compared to individuals who watched the neutral film ($b = 2.8$ [0.2–5.5], $p = 0.039$). Bayesian linear regression revealed that, given our data and a non-informative prior, the probability that this group difference is greater than 0 is 99%. There was a significant sex × film condition interaction on craving reactivity ($b = 5.0$ [0.03–10.0], $p = 0.049$). When analyzing the effect separately by sex, there was a main effect of the trauma condition on craving reactivity only for females ($b = 4.6$ [1.2–8.0], $p = 0.008$) but not for males ($b = -0.4$ [−4.1 to 3.3], $p = 0.812$) (Fig. 1). The effect of the trauma condition on craving reactivity was not moderated by harmful drinking ($b = 0.7$ [−4.5 to 6.0], $p = 0.778$).

Childhood trauma, stress reactivity, and craving reactivity

Craving reactivity in the trauma film condition increased with the number of reported childhood traumas in males ($b = 4.8$

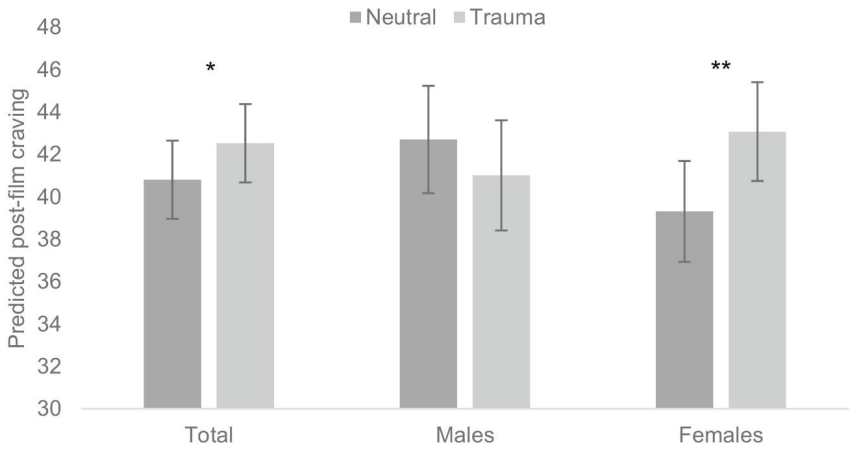

Fig. 1 Predicted self-reported craving (ACQ-SF-R score, range 12–84) in the trauma and neutral film conditions. Results from robust linear regressions, adjusted for baseline craving, alcohol use, and coping drinking motive

[2.5–7.1], $p < 0.001$) but not in females ($b = -1.3$ [−3.2 to 0.7], $p = 0.196$) (Fig. 2) with a significant three-way interaction sex × childhood traumas × film condition ($b = 8.3$ [4.4–12.1], $p < 0.001$). Bayesian linear regression revealed that given our data and a non-informative prior, the probability that this association is greater than 0 was 98% for males and 12% for females. The same pattern was observed for the association between physiological stress reactivity in the trauma film condition and the number of reported childhood traumas. In males, but not in females (p's > .459), the number of childhood traumas was positively associated with increase in HRR ($b = 3.0$ [1.2–4.7], $p = 0.001$) and SCR ($b = 0.3$ [0.0–0.7], $p = 0.050$), whereas CortR in the trauma condition decreased with increasing numbers of childhood traumas ($b = -62.4$ [−107.9 to −16.9], $p = 0.008$) (Fig. 3a–c). Bayesian linear regression revealed that given our data and a non-informative prior, the probability that these associations are greater (resp. lower for cortisol) than 0 was 98% for HRR, 93% for SCR, and 96% for CortR. Among these physiological measures associated with childhood traumas in males, SCR was also positively related to craving reactivity in the trauma film condition ($b = 1.7$ [0.1–3.2], $p = 0.035$) (Fig. 4). Bayesian linear regression revealed that the probability that this association is greater than 0 was 60%. After exclusion of two outliers (see Fig. 4) (which are down-weighted by robust linear regression), this probability increased to 89%. Self-reported anxiety was not associated with childhood traumas in males or females (p's > 0.347). The associations of childhood traumas with craving reactivity and stress reactivity measures in the trauma film condition did not differ by harmful drinking status (p's > .221).

Exploratory analyses: attention towards alcohol-related cues

We found no effect of acute trauma exposure on attention towards alcohol-related cues for males or females (p's > 0.659). There were also no interactions childhood traumas × film condition in males or females (p's > 0.246).

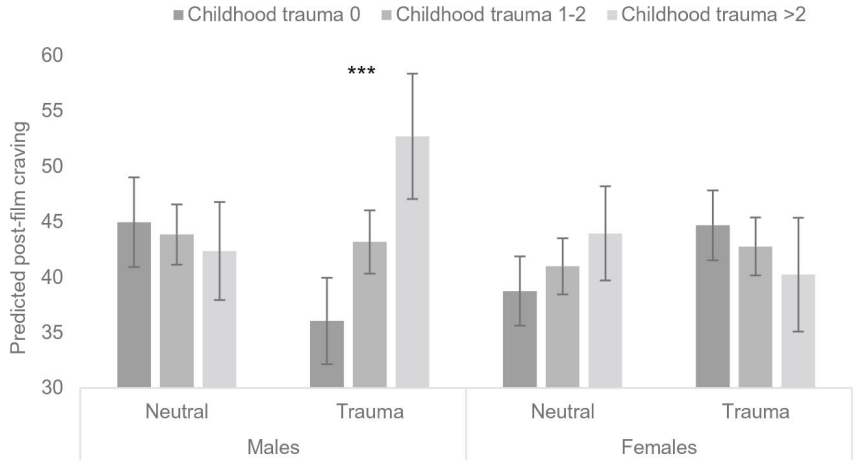

Fig. 2 Predicted self-reported craving (ACQ-SF-R score, range 12–84) in the trauma and neutral film conditions by number of reported childhood traumas. Results from robust linear regressions with number of childhood traumas (reported in the THQ) as dimensional predictor, adjusted for baseline craving, alcohol use, and coping drinking motive. Number of childhood traumas was categorized into 0, 1–2, and more than 2 traumas for illustrative purposes. *$p < .05$; **$p < .01$; ***$p < .001$

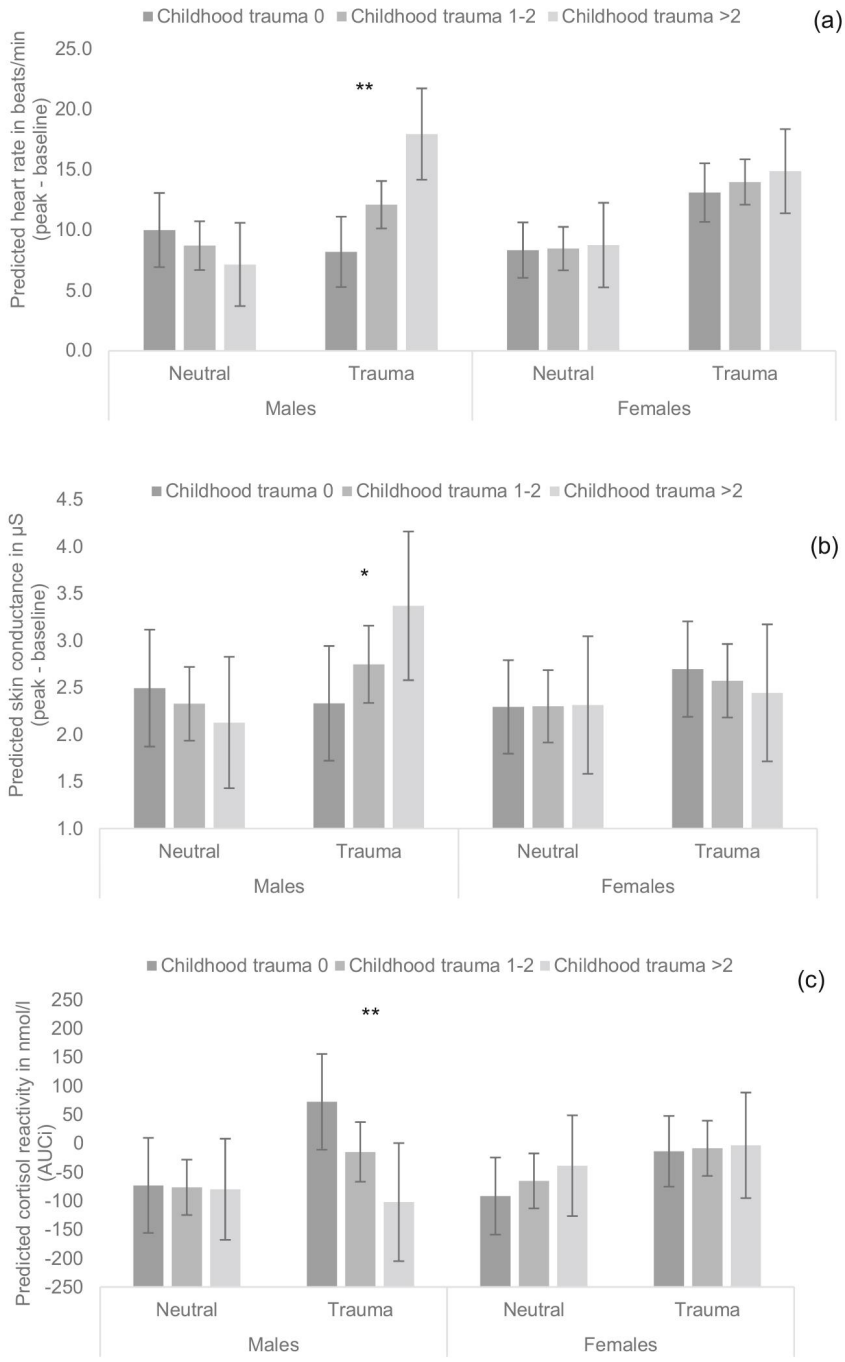

Fig. 3 Predicted stress reactivity in the trauma and neutral film conditions. **a** Heart rate. **b** Skin conductance. **c** Cortisol. Results from robust linear regressions with number of childhood traumas (reported in the THQ) as dimensional predictor, adjusted for alcohol use, trait anxiety, and emotional contagion. Number of childhood traumas was categorized into 0, 1–2, and more than 2 traumas for illustrative purposes. *$p < .05$; **$p < .01$

Discussion

This study investigated the effects of acute trauma exposure on alcohol craving in healthy individuals using a randomized laboratory controlled analogue design and, additionally, considering the potential roles of childhood traumas and stress reactivity. The main findings were as follows: (a) Craving increased in response to an acute analogue trauma compared to a neutral condition in females; (b) among males, trauma-induced craving reactivity increased with the number of reported childhood traumas; (c) among males, childhood traumas were further associated with altered peri-traumatic stress reactivity measures (HRR, SCR, CortR), of which SCR was also related to alcohol craving reactivity.

To our best knowledge, this is the first study showing that a laboratory traumatic stressor could be causally linked to subsequent increases in alcohol craving in healthy, non-abstinent individuals. This finding is in line with previous studies showing increased craving after exposure to trauma cues in alcohol-dependent individuals (Coffey et al. 2006, 2010; Kwako et al. 2015; Ralevski et al. 2016). However, the main effect of trauma exposure on craving reactivity was limited to female

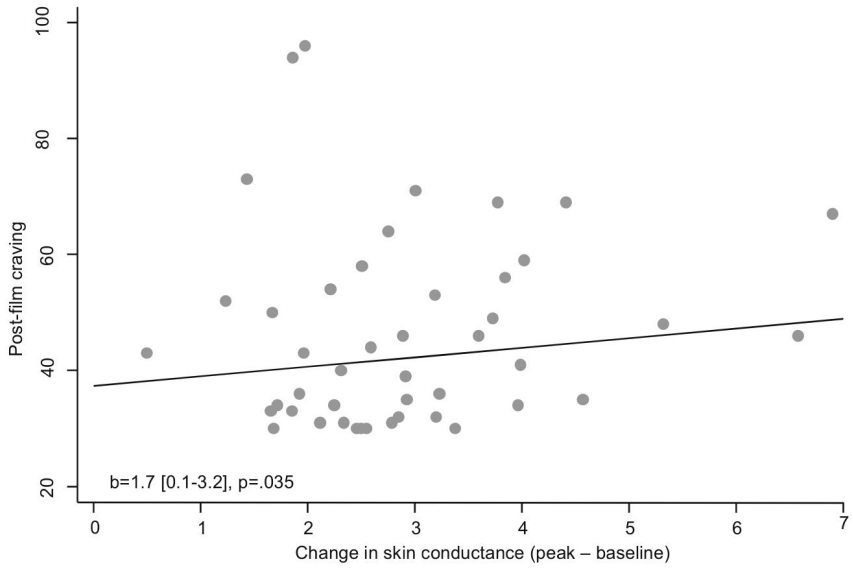

Fig. 4 Association between change in skin conductance and self-reported craving (ACQ-SF-R score, range 12–84) in the trauma film condition. Results from robust linear regressions, adjusted for baseline craving, sex, alcohol use, and coping drinking motive

participants. It could be speculated that females might have reacted more intensely to the rape scene that was used as a traumatic stressor in our study. However, we only found respective sex differences in reported state anxiety but not in the physiological stress markers. A previous validation study of the used film material also showed no significant sex differences in stress reactivity (Weidmann et al. 2009). There is evidence that women are more vulnerable to traumatic stress than men and therefore more prone to adverse trauma-related consequences (Hagborg et al. 2017). This has also been observed for substance use and craving following traumatic and non-traumatic stressors (Danielson et al. 2009; Saladin et al. 2012; Gibbons et al. 2012). This effect could be mediated by a higher probability of risk genes (Ressler et al. 2011) or differences in biological stress systems (e.g., higher sensitivity of the adrenal cortex) (Roelfsema et al. 1993) in women. However, we cannot exclude the possibility that a higher identification with a female victim in the film material among female study participants has led to the observed findings. Thus, there is need for a replication of the found sex differences using traumatic material, which is less likely to elicit sex-specific responses.

It is also noteworthy that the effect of the trauma film on craving reactivity was independent from harmful drinking status. This finding is in line with the idea that traumatic stress can sensitize alcohol-related motivational systems at all levels of alcohol use (Lijffijt et al. 2014). However, it is possible that harmful drinking has sex-specific effects, which we were not able to analyze due to the limited sample size.

Unlike in females, the effect of acute trauma on craving reactivity in males was dependent on the experience of childhood traumas such that craving reactivity induced by the trauma film increased with the number of reported childhood events. Among males, childhood traumas were also associated with altered stress reactivity with increased autonomic (HR, SCR) and decreased endocrine reactivity (CortR). Of these stress reactivity measures, only SCR was also related to craving reactivity after the trauma film. Thus, these findings might suggest that sympathetic stress reactivity is involved in the mediation of the observed association between childhood traumas and trauma-induced craving reactivity found in male participants, e.g., via its association with impaired inhibitory control and shift to habitual behavior (Otto et al. 2013; Allen et al. 2014). The association between SCR and craving reactivity was, however, only modest (see Fig. 4) and HRR was not related to craving reactivity. Since HRR (other than SCR) is also modulated by vagal tone (parasympathic activity), this pattern suggests that primarily sympathetic activity is involved in the association between childhood traumas and craving reactivity in males. Due to the small effects and specific associations, these findings should be seen as preliminary and other mediators might be more relevant. Although CortR has also been reported as an important link between stress exposure and alcohol use (Koob 2009; Spanagel et al. 2014), relevant changes in the reward systems induced by glucocorticoid increase probably develop later than 30 min post-film (Joëls and Baram 2009), which is when craving was assessed. This could explain why CortR did not affect craving reactivity in the current study.

Our findings correspond well with the large body of evidence for the sensitization of biological and motivational systems through cumulative stress (Kim et al. 2014; Lijffijt et al. 2014) suggesting moderating effects of childhood adversities for the effect of later trauma exposure on alcohol use outcomes (Clarke-Walper et al. 2014; Keyes et al. 2014) and stress reactivity (Muehlhan et al. in press, 2017; Bunea et al. 2017). However, it seems surprising that this moderation was only seen in males in our study, especially because craving reactivity was higher in females than in males. Only a few studies have examined the association between acute trauma

and craving reactivity so far and we can only speculate about possible reasons at this point. As females showed a stronger main effect of trauma exposure on craving reactivity than males, there might be a ceiling effect in trauma-induced craving reactivity preventing a further increase among females exposed to childhood traumas. Since only a small proportion of males experienced multiple childhood traumas, it is still plausible that the main effect of acute trauma on craving reactivity was higher in females despite the association between childhood traumas and craving reactivity in males. Another likely explanation could lie in relevant differences in number, type, or timing of childhood traumas between males and females. While we could not find sex differences in the number of childhood traumas or the age at first childhood trauma exposure, males were more likely to experience crime victimization during childhood. Thus, the male subsample might have been somewhat more likely to have been exposed to interpersonal childhood traumas, a trauma type showing strong associations with a sensitization of the sympathetic nervous system and addictive behaviors, particularly when experienced during childhood (Konkolÿ Thege et al. 2017). Further studies are needed to elucidate the sex differences observed in this study.

In an exploratory analysis, we found no evidence for an association between acute trauma exposure and attention towards alcohol-related cues and no moderation by childhood trauma. This finding contradicts both theoretical models, which assume an interplay between increased attention towards alcohol-related cues and alcohol craving (Franken 2003), and previous studies showing increased alcohol-related attentional bias following stress exposure (Field and Quigley 2009). However, a meta-analysis (Field et al. 2009) suggested that the association between attentional bias and craving is only weak, particularly for alcohol craving. Moreover, the visual probe task, although widely used, has recently been criticized because of its poor reliability (Ataya et al. 2012), which might have contributed to the null finding in our study.

This study has several limitations. First, we assessed the association between trauma and alcohol craving within a laboratory model of acute trauma exposure in healthy individuals. While this approach allows rigorous experimental manipulation, the findings might not be transferable to the association between actual cumulative traumatic events and craving. Thus, the clinical implications of our findings have still to be determined. Moreover, the estimated effects of childhood trauma in this study are likely to be conservative since sexual and violent traumas had to be excluded. Second, childhood traumas were assessed retrospectively, which can introduce recall bias with, however, small risks of false positives (Hardt and Rutter 2004). Recall biases also increase with distance to trauma exposure (Green et al. 2010) and should be limited in this relatively young sample. Third, the limited sample size leads to small group sizes in the moderation analyses by sex. To alleviate this problem, we used additional Bayesian linear regression with a flat prior that provides more realistic and stable estimates when sample sizes are small (Baldwin and Larson 2017). Nevertheless, future studies are needed to replicate these findings in larger samples and verify the currently observed associations in individuals with actual trauma, e.g., in the immediate aftermath of accidents. Moreover, repeated measures of stress-reactivity and craving could help to investigate their link beyond the immediate post-traumatic reaction.

Considering these limitations, the findings of this study have important implications. By demonstrating that an acute trauma can directly elevate alcohol craving in healthy individuals within an experimental laboratory model of trauma exposure, we provide evidence for a potential causal link between traumatic experiences and the desire for alcohol use, which might be a key mechanism underlying initiations and escalation of alcohol use after trauma exposure. While this association seems to be stronger in females, males might still be at risk in case of the presence of other vulnerability factors such as a history of childhood traumas that is altering the trauma-associated sympathetic stress reactivity as a potential underlying mechanism. Replications of these findings in further studies with increased external validity of measures of trauma exposure and alcohol use (e.g., in high-risk samples) are needed. Future studies might also benefit from a higher variability of traumatic stressors and the use of within-subject designs. In the long term, these findings could help to identify individuals at risk for alcohol use problems following trauma exposure and to provide early interventions for vulnerable individuals.

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Compliance with ethical standards

The entire study procedure was approved by the Ethics Board of the Technische Universität Dresden (EK 23022008).

Conflict of interest The authors declare that they have no conflict of interest.

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6 Biological stress indicators as risk markers for increased alcohol use following traumatic experiences

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Biological stress indicators as risk markers for increased alcohol use following traumatic experiences

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ABSTRACT

Alcohol misuse is a common sequela of traumatic event experiences causing considerable morbidity and mortality. Although biological stress indicators have been identified as useful risk markers for the development of trauma-related disorders, no such biological indicators exist for the risk of increased alcohol use after trauma exposure. This is the first study to prospectively investigate the predictive value of long-term cortisol levels and acute stress reactivity for the risk of increased alcohol use following traumatic events. Male soldiers were examined before and 12 months following deployment using a standardized diagnostic interview. We analyzed the moderating role of baseline hair cortisol concentrations (HCCs, $n = 153$) as well as baseline salivary cortisol and alpha-amylase stress reactivity in response to a laboratory stressor ($n = 145$) in the association between new-onset traumatic events (according to the DSM-IV A1 criterion) and subsequent daily alcohol use. No main effects of pre-traumatic HCC or salivary stress markers on subsequent change in alcohol use were observed. However, we found that with decreasing HCC, the number of new-onset traumatic events was more strongly associated with subsequent alcohol use independent from changes in posttraumatic stress disorder symptoms. No such relation was seen for the acute stress reactivity data. Taken together, this study provides first evidence suggesting that individual differences in long-term cortisol regulation are involved in the association between traumatic experiences and subsequent alcohol use. HCC may thus serve as a potential target in the early identification of individuals vulnerable for increased alcohol use following traumatic events.

Keywords Alcohol, cortisol, stress, trauma, TSST.

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INTRODUCTION

Traumatic events have a high prevalence worldwide with, on average, 70 percent experiencing at least one and 30 percent experiencing four or more events (Benjet *et al.* 2015). These rates can reach up to 90 percent in specific populations such as military personnel (Hoge *et al.* 2004; Wittchen *et al.* 2012a). The experience of traumatic events is associated with an elevated risk for various mental health problems (Ayazi *et al.* 2014; Maercker *et al.* 2004). Beyond posttraumatic stress disorder (PTSD), particularly strong relationships have been revealed with alcohol misuse. There are a vast number of epidemiological studies showing both cross-sectional and longitudinal associations between trauma exposure in both childhood and adulthood and the risk for increased alcohol use, excessive drinking and alcohol use disorders (Kendler *et al.* 2000; Keyes *et al.* 2011; Stewart 1996). Given that alcohol consumption is one of the most important risk factors for chronic disease and injury (Rehm *et al.* 2009), the early identification of individuals at high risk for increased alcohol use following traumatic events is of vital importance.

In the past decades, the self-medication hypothesis has been the predominant model to explain the relation between traumatic experiences and alcohol use, proposing that alcohol is used to cope with adverse psychological symptoms caused by the traumatic event (Khantzian 1997). This model is supported by many empirical findings showing a relationship between trauma-related disorders and alcohol use (Debell *et al.* 2014; Trautmann *et al.* 2015). However, some epidemiological and experimental findings contradict this notion and suggest that self-medication is unable to fully explain the link between

trauma exposure and alcohol use (Fetzner *et al.* 2011; Stevens *et al.* 2008). Recently, more comprehensive models have been developed that, unlike the self-medication hypothesis, are not limited to a behavioral level and include additional psychological and physiological processes (Lijffijt *et al.* 2014; Schepis *et al.* 2011). A core assumption of these models is that alterations in stress systems following chronic or repeated stressful experiences constitute a vulnerability factor for the development of subsequent alcohol use problems. These alterations can trigger increases in mesolimbic dopamine concentrations, a sensitization of motivational systems and changes in the processing of alcohol-related stimuli; mechanisms that are known to be closely related to alcohol use and the progression to alcohol use problems (Lijffijt *et al.* 2014; Spanagel *et al.* 2014). In fact, there is evidence for an association between alcohol consumption and dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis in terms of both decreased basal cortisol levels and cortisol response to acute stressors (Adinoff *et al.* 2005; Badrick *et al.* 2008), although findings are not entirely consistent (Boschloo *et al.* 2011; Gianoulakis *et al.* 2003). There is also first evidence indicating that flatter diurnal cortisol slopes prospectively predict alcohol use in adolescents (Ruttle *et al.* 2015). In summary, both recent theoretical developments and initial empirical findings suggest that cortisol alterations may have the potential to predict the risk of posttraumatic increases in alcohol consumption. Such changes may be the result of cumulative exposure to stressful events (Steudte *et al.* 2013, 2016), i.e. initial HPA axis dysregulation might be exacerbated by further stressful/traumatic experiences. Based on this, we hypothesize that pre-existing abnormalities in cortisol activity predict increased alcohol use following new-onset traumatic experiences. This might also be true for alterations in autonomic nervous system functioning that have also been related to alcohol use (e.g. Krystal & Neumeister 2009). Biological markers have been successfully studied for other stress-related disorders, such as PTSD (Zoladz & Diamond 2013). For example, reduced glucocorticoid signaling before and shortly after trauma exposure was found to be a risk factor for PTSD development (van Zuiden *et al.* 2012a). However, respective data for the risk of increased alcohol consumption following traumatic events are outstanding.

To our best knowledge, this is the first study to prospectively investigate the predictive value of biological stress indicators for the risk of increased alcohol use following traumatic event exposure. For this, we particularly focused on hair cortisol concentrations (HCCs) as a reliable and valid measure of long-term integrated cortisol secretion (Stalder & Kirschbaum 2012) as well as on the salivary cortisol and alpha-amylase response to a laboratory stressor as measures of acute stress reactivity.

METHODS AND MATERIALS

Data were drawn from a German prospective-longitudinal study on mental health consequences of military deployment. Assessments were conducted directly before deployment (Time 1) and 12 months after return from deployment (Time 2). A detailed description of the design and methods are provided elsewhere (Steudte-Schmiedgen *et al.* 2015; Wittchen *et al.* 2012b). The study procedure was approved by the Ethics Board of the Technische Universität Dresden (EK 72022010).

Sampling

The total baseline sample of this study consisted of 618 soldiers from the German International Security Assistance Force mission in Afghanistan in 2011/2012. Because of the low percentage of female soldiers in the German International Security Assistance Force contingents, only male soldiers were sampled. In a subsample of 281 subjects, hair strands were collected for the analysis of long-term integrated cortisol levels (HCC subsample). This subsample was restricted to participants with hair of at least 2 cm length at the posterior vertex region of the scalp and without any signs of hair loss or baldness. Another subsample of 296 subjects participated in the Trier social stress test (TSST; Kirschbaum *et al.* 1993) at baseline for the analysis of acute stress reactivity (TSST subsample). Assignment to the TSST can be considered as random because of logistic restrictions (availability of assessment rooms). Soldiers were excluded if they exhibited any of the following criteria: severe physical disease (e.g. cancer, adrenocortical dysfunction and neurological diseases) over the past 5 years, use of psychotropic medications (e.g. antidepressants) within the past 6 months (based on self-report), lifetime diagnosis psychosis or bipolar disorder. This resulted in an exclusion of 37 subjects in the HCC and 33 subjects in the TSST subsample. After further exclusion of statistical outliers (see thereafter), baseline HCC data were available for 242 and TSST data for 258 subjects. Among these subjects with baseline samples, follow-up information on daily alcohol use could be obtained for 153 subjects of the HCC and 145 subjects of the TSST subsample (with 85 subjects overlapping between both subsamples). We conducted a series of analyses to test for selective non-participation. In logistic regression analyses, we tested whether non-participation at follow-up, non-availability of TSST data and non-availability of HCC data could be predicted by the following baseline variables that are assumed to affect observed associations between stress indicators and alcohol use: age, education, a history of any mental disorder, alcohol use (g/day), PTSD symptoms and the

number of prior traumatic events. No significant associations were found ($P > 0.05$), except for higher PTSD symptom scores among subjects not available for the TSST (OR = 1.1 95 percent CI 1.0–1.1 $P = 0.047$). All results of analyses for selective dropout are shown in Supporting Information Table S1.

Assessment of alcohol use

Alcohol use was assessed with the substance use section of the Munich-Composite International Diagnostic Interview (Wittchen & Pfister 1997), a fully standardized reliable and valid diagnostic interview (Lachner *et al.* 1998; Reed *et al.* 1998). Both amount (drinks consumed in a typical drinking occasion) and frequency of alcohol use in the preceding 12 months were assessed. Average daily alcohol use was calculated using information on the amount of ethanol in gram per occasion (one drink equals 9 g of ethanol) and the frequency of drinking occasions.

Assessment of trauma-related variables

Traumatic events were assessed within the Munich-Composite International Diagnostic Interview at baseline and 12-month post-deployment follow-up. Participants responded to a list of 28 military and non-military events that met the A1 criterion of the DSM-IV (Supporting Information Table S2). PTSD symptoms were assessed with the civilian version of the PTSD checklist (Weathers *et al.* 1991). Maltreatment in childhood was measured with the childhood trauma questionnaire (CTQ, Bernstein *et al.* 2003).

Assessment of biological stress indicators

Long-term integrated cortisol levels

We used the analysis of HCC as an index of long-term integrated cortisol secretion. Over the past decade, evidence has accumulated supporting HCC in terms of its overall validity, reliability and robustness against potential confounders (review: Stalder & Kirschbaum 2012). Hair strands (~3 mm diameter) were cut scalp-near from a posterior vertex position. HCC in the proximal 2-cm hair segment were assessed reflecting integrated cortisol secretion over the 2-month period prior to hair sampling (Stalder & Kirschbaum 2012). Cortisol concentrations were quantified via liquid chromatography tandem mass spectrometry (as in Steudte-Schmiedgen *et al.* 2015), which is considered the current gold standard methodology for hair steroid analysis (Gao *et al.* 2013). Intra-assay and inter-assay coefficients of variation have been shown to range between 3.7 and 8.8 percent (Gao *et al.* 2013).

Indicators of stress reactivity

The TSST (Kirschbaum *et al.* 1993) is an effective standardized protocol for the reliable induction of acute psychosocial stress under laboratory conditions, e.g. leading to enhanced activity of the HPA axis and the autonomic nervous system (Foley & Kirschbaum 2010). In brief, the TSST consists of a public speaking (5 minutes) and a mental arithmetic task (5 minutes) performed in front of two evaluators. Participants were instructed to refrain from smoking, eating and drinking anything but water 60 minutes prior to the TSST. Saliva samples were collected immediately before the TSST as well as 1, 10 and 20 minutes after the TSST using Salivettes 'code blue' devices (Sarstedt, Germany). Samples were stored at −20 °C in a laboratory freezer until analyses. After thawing, saliva samples were centrifuged for 10 minutes at 4000 r.p.m. All samples were analyzed for concentrations of salivary cortisol and alpha-amylase providing sensitive markers for stress-induced activity of the HPA axis and the autonomic nervous system, respectively. Salivary cortisol levels were determined by using a commercially available luminescence assay (LIA, IBL-Hamburg, Germany), while concentrations of salivary alpha-amylase were detected by using an in-house enzyme kinetic method according to the protocol described elsewhere (Rohleder & Nater 2009). For cortisol and alpha-amylase, inter-assay coefficients of variation were less than 5.29 and 10 percent, respectively. Salivary cortisol ($t = 12.5$ d.f. = 144 $P < 0.001$), alpha-amylase levels ($t = 8.2$ d.f. = 143 $P < 0.001$) and self-reported agitation ($t = 8.2$ d.f. = 134 $P < 0.001$) were found to increase while self-reported mood declined ($t = 8.3$ d.f. = 137 $P < 0.001$) in response to the TSST.

Statistical analysis

Because HCC, salivary cortisol and alpha amylase data were not normally distributed, log transformations were applied to reduce skewness. For HCC analyses, data from three participants were excluded because of outlying values of more than three standard deviations (SDs) above the mean. In the TSST sample, data from five participants were excluded because of outlying values of more than three SDs above the mean. We calculated composite measures of the entire cortisol secretion during the TSST [area under the curve with respect to ground (AUC_G)] and the cortisol stress reactivity [area under the curve with respect to increase (AUC_I)] (Pruessner *et al.* 2003). As dependent variable, we used past 12 months average daily alcohol consumption assessed at Time 2 adjusting for baseline values. The difference in daily alcohol use between Times 1 and 2 was tested using paired *t*-tests. Linear regression analyses were applied for the prediction of alcohol use at Time 2 by HCC,

salivary cortisol and alpha-amylase (AUCs) measured at Time 1. For graphical visualization, continuous HCC scores were dichotomized using median split. We also applied two sensitivity analyses for the reactivity measures to examine the stability of the results. With regard to alpha-amylase, we run the same analysis with peak minus baseline levels instead of AUC measures. With regard to salivary cortisol levels, not all individuals responded to the TSST with an increase of 1.5 nmol/l compared with baseline (Miller *et al.* 2013). Therefore, we conducted all analyses including salivary cortisol measures both with the full TSST sample as well as a subsample excluding non-responders (n = 10). Because childhood adversities have been shown to be related to both biological processes and alcohol use (Keyes *et al.* 2014; Teicher & Samson 2013), we additionally analyzed respective associations with CTQ scores. Statistical inference was based on the robust Huber–White sandwich estimator of standard errors (Royall 1986) because this revealed considerably different results compared with conventional model-based estimation of standard errors indicating that the robust method should be preferred. For the analysis of interactions between biological stress indicators and new-onset traumatic events in the follow-up period, we fitted separate models that added the main effect term of the traumatic event variable and the interaction term with the respective stress indicator. Specifically, three sets of models were fitted: The first model yielded crude associations. The second model was adjusted for age (interval scaled), education (high, middle and low) and previous traumatic events. In the third model, associations were additionally adjusted for change in PTSD symptoms in the follow-up period. This was performed because previous studies have linked the examined potential markers to the development of PTSD symptoms (Steudte-Schmiedgen *et al.* 2015), and we aimed to

Table 1 Demographic, trauma, alcohol-related and stress-related sample characteristics.

	HCC sample	TSST sample
	(n = 153)	(n = 145)
Demographics		
Age, mean (SD)	28.8 (6.2)	28.6 (5.8)
Education, n (%)		
Low	21 (13.7)	31 (21.4)
Middle	104 (68.0)	88 (60.9)
High	28 (18.3)	26 (17.9)
BMI, mean (SD)	24.8 (2.7)	24.7 (2.6)
Trauma-related		
No. of previous traumatic events, mean (SD)	1.9 (2.1)	1.6 (1.8)
No. of new-onset traumatic events, n (%)		
0	56 (36.6)	58 (40.0)
1	52 (34.0)	46 (31.7)
2–3	35 (22.9)	33 (22.8)
4+	10 (6.5)	8 (5.5)
PCL score at BL, mean (SD)	1.5 (3.3)	1.3 (3.2)
PCL score at FU, mean (SD)	2.3 (5.4)	1.8 (4.6)
Alcohol-related		
History of alcohol dependence, n (%)	5 (3.3)	2 (1.4)
Daily alcohol consumption in g at BL, mean (SD)	16.5 (25.0)	13.3 (20.1)
Daily alcohol consumption in g at FU, mean (SD)	13.1 (16.4)	11.8 (16.6)
Stress-related (at BL)		
Salivary cortisol in nmol/l, mean (SD)		
−1 minute before TSST	9.8 (4.6)	10.1 (5.1)
+1 minute after TSST	17.5 (9.2)	17.3 (9.0)
+10 minutes after TSST	24.0 (12.8)	24.4 (12.4)
+20 minutes after TSST	22.5 (12.3)	23.0 (12.0)
HCC in pg/mg, mean (SD)	3.4 (2.6)	3.3 (2.2)
Salivary alpha amylase in U/ml, mean (SD)		
−1 minute before TSST	184 (171)	169 (139)
+1 minute after TSST	240 (177)	231 (169)
+10 minutes after TSST	189 (142)	170 (128)
+20 minutes after TSST	173 (139)	156 (119)

BL = baseline; BMI = body mass index; FU = follow-up; HCC = hair cortisol concentration; PCL = posttraumatic stress disorder checklist; SD = standard deviation; TSST = Trier social stress test.

exclude the possibility that changes in alcohol use just reflect the self-medication of PTSD symptoms. Associations between stress indicators and previous traumatic events reported at baseline were also analyzed with linear regressions. We report the analogous three models as for the prediction of alcohol use except for the third model that is adjusted for daily alcohol use in the previous year at baseline instead of PTSD symptoms. Statistical significance was evaluated at the two-sided 5 percent level. In graphical illustrations of results, the procedure MARGINS was used to calculate predicted probabilities. All analyses were conducted with STATA 12.1 (Stata Corp. 2012).

RESULTS

Sample characteristics

Table 1 summarizes sample characteristics for both the HCC and the TSST sample. The majority of soldiers experienced at least one new-onset A1 traumatic event during the follow-up period (HCC sample: 63.4 percent; TSST sample: 60.6 percent). The mean number of new-onset traumatic events was 1.3 (SD = 1.6) for the HCC and 1.2 (SD = 1.5) for the TSST sample. Detailed information on the types of the experienced events is provided in Supporting Information S2. In both subsamples, change in daily alcohol use from Times 1 to 2 was not found to be statistically significant (TSST sample: t = 0.9 d.f. = 144 P = 0.378; HCC sample: t = 0.9 d. f. = 152 P = 0.074).

Baseline cross-sectional associations

Table 2 shows associations between biological stress indicators and previous traumatic events reported at baseline. After adjusting for age, education and alcohol use at baseline, both HCC (β = −0.12, 95 percent CI −0.24 to 0.00, P = 0.050) and AUC_G salivary cortisol (β = −31.09, 95 percent CI −58.68 to −3.50, P = 0.027) were related to the number of previous traumatic events. Specifically, HCC and AUC_G salivary cortisol were found to decrease with increasing number of traumatic events (Fig. 1a & b). Alpha-amylase was not related to the number of previous traumatic events. Also, none of the biological stress indicators were related to childhood adversities. Again, comparable results were found for peak minus baseline levels and AUC measures (alpha-amylase) as well as for the full TSST sample and the subsample excluding non-responders (salivary cortisol). Alcohol use reported at baseline was not associated with any biological stress indicator or with childhood adversities.

Prospective associations between stress indicators and change in alcohol use

Table 3 reports associations between new-onset traumatic events, the examined biological stress indicators at baseline and alcohol use at Time 2 for both main effects and interactions. New-onset traumatic events were not predictive of alcohol use at Time 2. Moreover, neither HCC nor markers of acute stress reactivity were significantly related to alcohol use. However, the interaction between HCC and the number of new-onset traumatic events predicted alcohol use (β = −4.80 change in association per increase by one unit of HCC, 95 percent CI −8.55 to −1.05, P = 0.012). Specifically, the number of traumatic events was associated with higher alcohol use in individuals with low but not in individuals with high HCC (Fig. 2). This association was confirmed while adjusting for age, education, previous traumatic events and change in PTSD symptoms in the follow-up period (Table 2). All other interactions did not reach statistical significance. Sensitivity analyses showed comparable results for peak minus baseline levels and AUC measures (alpha-amylase) as well as for the full TSST sample and

Table 2 Prediction of biological indicators of stress from previous traumatic events reported at baseline.

	Model I			Model II			Model III		
	β	95% CI	*P*	*β*	95% CI	*P*	*β*	95% CI	*P*
Long-term cortisol									
HCC BL	−0.10	−0.22 to 0.01	0.081	−0.12	−0.24 to 0.00	0.058	−0.12	−0.24 to 0.00	0.050
Stress reactivity									
Cortisol AUC_I	−4.63	−23.71 to 14.44	0.632	−8.27	−28.13 to 11.58	0.411	−8.44	−28.47 to 11.59	0.406
Cortisol AUC_G	−23.75	−50.56 to 3.06	0.082	−30.96	−58.33 to −3.59	0.027	−31.09	−58.68 to −3.50	0.027
Amylase AUC_I	59.72	−107.13 to 226.57	0.480	49.88	−123.20 to 222.95	0.570	48.03	−125.80 to 221.86	0.586
Amylase AUC_G	70.86	−328.21 to 469.93	0.726	66.95	−352.17 to 486.07	0.753	65.59	−356.69 to 487.88	0.759

AUC_G = area under the curve with respect to the ground; AUC_I = area under the curve with respect to increase; BL = baseline; CI = confidence interval; HCC = hair cortisol concentration; model I = crude associations; model II = adjusted for age and education; model III = model II + adjusted for alcohol use at BL; TSST = Trier social stress test.

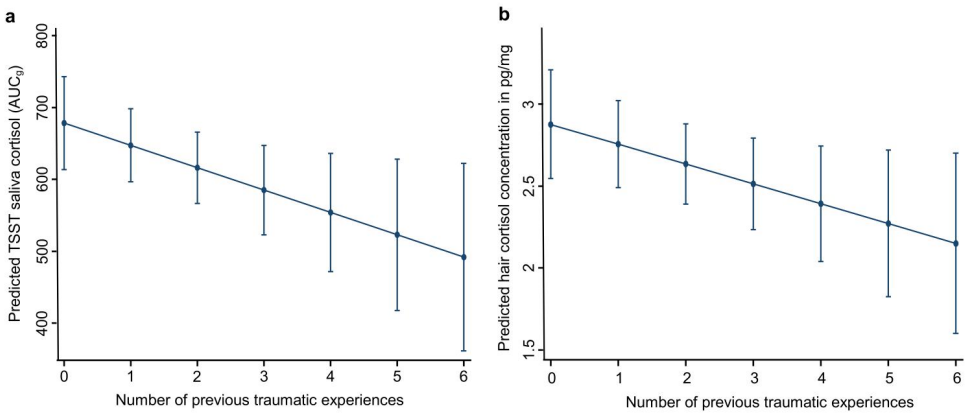

Figure 1 (a) Association between Trier social stress test (TSST) area under the curve with respect to the ground (AUC_G) salivary cortisol and previous traumatic events. Result from robust linear regression analysis adjusted for age, education and alcohol use at baseline including 95 percent confidence intervals. Association is statistically significant ($P < 0.05$). (b) Association between hair cortisol concentration and previous traumatic events. Result from robust linear regression analysis adjusted for age, education and alcohol use at baseline including 95 percent confidence intervals. Association is statistically significant ($P < 0.05$) [Colour figure can be viewed at wileyonlinelibrary.com]

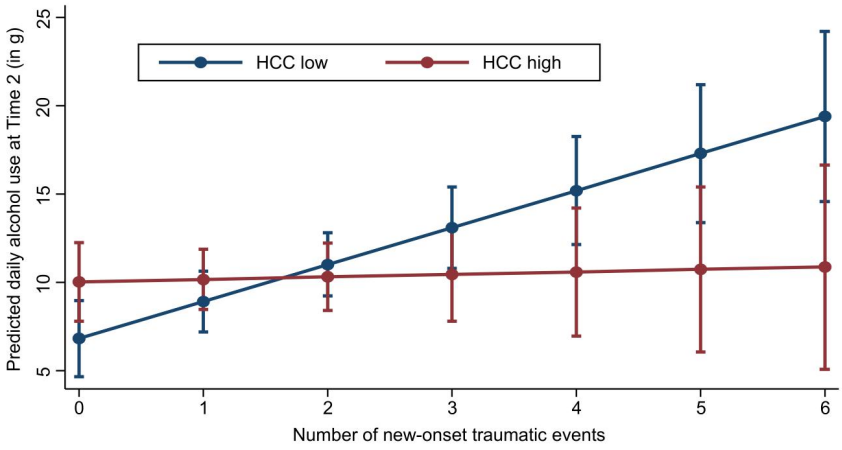

Figure 2 Interaction between hair cortisol concentration (HCC) and traumatic events predicting daily alcohol use. Results from robust linear regression analysis adjusted for age, education, previous traumatic events, baseline alcohol use and change in PTSD symptoms in the follow-up period including 95 percent confidence intervals. In this figure, HCC was dichotomized using median split. Interaction between HCC and traumatic events is statistically significant ($P < 0.05$) [Colour figure can be viewed at wileyonlinelibrary.com]

the subsample excluding non-responders (salivary cortisol).

DISCUSSION

Using data from a prospective-longitudinal study in deployed military personnel, we investigated the predictive value of long-term HCC and stress-induced salivary cortisol and alpha-amylase activity for the risk of increased alcohol consumption following traumatic event exposure. The main finding was that with lower baseline HCC, the number of new-onset traumatic events experienced in the follow-up period was more strongly related to subsequent daily alcohol use.

While HCC moderated the association between new-onset traumatic events and alcohol use, new-onset traumatic events alone did not predict subsequent alcohol use. Thus, our findings support the assumption that individual differences in HPA axis activity, at least partially resulting from previous traumatic events, might be a key factor in the link between traumatic experiences and alcohol use risk (Lijffijt *et al.* 2014). This is very similar to what has been observed for the risk of PTSD development after trauma exposure (Resnick *et al.* 1995; Steudte-Schmiedgen *et al.* 2015). Alterations in cortisol levels might therefore constitute a transdiagnostic risk factor for the development of adverse psychological consequences after trauma exposure. However, the found associations in our study were independent from changes in PTSD symptoms suggesting different pathways.

For the association between HCC, trauma exposure and alcohol use, the close interaction between the HPA axis and the dopaminergic reward system might be seen as a potential underlying mechanism. It could be speculated that decreased HPA functioning operates jointly with decreased dopaminergic signaling within the reward circuitry (Rasheed *et al.* 2012; Spanagel *et al.* 2014). Given this assumption, reduced reward processing (e.g. in social interactions) might be compensated by the reinforcing effects of alcohol consumption. It

Table 3 Prediction of increase in daily alcohol consumption from new-onset traumatic events and biological indicators of stress.

	Model I			Model II			Model III		
	β	95% CI	*P*	*β*	95% CI	*P*	*β*	95% CI	*P*
New-onset traumatic events[a]	−0.10	−0.79 to 0.59	0.773	−0.02	−0.75 to 0.71	0.954	0.23	−0.57 to 1.02	0.578
Long-term cortisol									
HCC BL	2.34	−4.13 to 8.80	0.476	2.11	−4.65 to 8.87	0.539	1.79	−4.95 to 8.54	0.600
HCC BL × new-onset traumatic events	−4.80	−8.55 to −1.05	0.012	−5.03	−9.06 to −1.01	0.015	−6.03	−9.93 to −2.13	0.003
Stress reactivity									
Cortisol AUC_I	0.34	−5.60 to 6.28	0.909	−0.26	−6.48 to 5.96	0.935	−0.89	−7.48 to 5.71	0.791
Cortisol AUC_G	1.52	−3.22 to 6.27	0.527	1.61	−3.58 to 6.81	0.540	1.01	−4.27 to 6.29	0.706
Amylase AUC_I	−0.28	−1.16 to 0.60	0.533	−0.02	−1.07 to 1.03	0.974	−0.01	−1.05 to 1.02	0.982
Amylase AUC_G	−0.49	−1.76 to 0.79	0.452	−0.53	−1.83 to 0.77	0.424	−0.21	−1.59 to 1.17	0.763
Cortisol AUC_I × new-onset trauma	−0.09	−5.08 to 4.91	0.973	0.20	−4.98 to 5.37	0.941	−0.28	−5.80 to 5.23	0.919
Cortisol AUC_G × new-onset trauma	−0.28	−3.40 to 2.81	0.859	−0.18	−3.54 to 3.19	0.917	−1.66	−5.26 to 1.94	0.363
Amylase AUC_I × new-onset trauma	−0.75	−1.73 to 0.23	0.131	−0.73	−1.70 to 0.25	0.143	−0.75	−1.73 to 0.23	0.131
Amylase AUC_G × new-onset trauma	−0.87	−1.81 to 0.08	0.073	−0.75	−1.73 to 0.23	0.134	−0.87	−1.81 to 0.08	0.073

[a]Results among the TSST subsample. Similar results were observed in the HCC subsample (data available on request). AUC_I = area under the curve with respect to increase; AUC_G = area under the curve with respect to the ground; BL = baseline; CI = confidence interval; HCC = hair cortisol concentration; model I = crude associations; model II = adjusted for age, education and previous traumatic events; model III = model II + adjusted for change in PTSD symptoms between BL and FU; PTSD = posttraumatic stress disorder; TSST = Trier social stress test.

might be also possible that individuals with attenuated long-term cortisol secretion show higher stress reactivity during traumatic events compared with those with elevated cortisol levels (McEwen 2000; Stephens & Wand 2012). Because of the stress dampening effects of alcohol, an enhanced responsivity of the HPA axis might also support drinking. Both assumptions are in line with the self-medication hypothesis and recent theoretical models (Khantzian 1997; Schepis *et al.* 2011). Longitudinal research combining long-term measures of cortisol secretion with other established measures of HPA axis activity is needed to shed light on the precise origin and onset of these biological alterations in response to trauma and their interplay.

In contrast to long-term cortisol dysregulation, we did not find evidence for a prospective association between measures of acute stress reactivity and the risk for increased alcohol use after traumatic event exposure. This is in line with the assumption that long-term changes in neuroendocrine systems might be more important for disease risks than alterations in acute response to a single stressor (Stalder & Kirschbaum 2012) and supports previous findings on diverging information arising from HCC and other cortisol measures in clinical populations (Steudte *et al.* 2011, 2013, 2016). However, it should be noted that short-term biological measures in saliva can be influenced by daily fluctuations and situational factors (e.g. food intake, smoking, mood and setting variables) (Stalder & Kirschbaum 2012) that might have introduced measurement error that is likely to being independent from outcome, what in turn yields downward bias in estimates of associations. It is also noteworthy that, in contrast to the overall tendency of previous evidence, we found no associations between childhood adversities and biological stress indicators or alcohol use. This might be explained by relatively low CTQ scores in our sample. Moreover, prior evidence suggests that specific adversities during sensitive developmental periods can explain biological and psychological changes better than the cumulative exposure measured with the CTQ (Teicher & Samson 2013).

Our findings might have significant implications for the identification of individuals being vulnerable for increased alcohol use following trauma exposure. Considering the methodological advantages of hair cortisol analysis (i.e. retrospectivity, integrative nature and robustness to unwanted influences) (Steudte-Schmiedgen *et al.* 2016), it is conceivable that HCC may be a valuable target for a risk marker for alcohol use in populations at high risk for traumatic event exposure. This might be particularly effective for individuals with prior trauma history as it has frequently been observed that trauma exposure *per se* is reflected in attenuated HCC patterns (Hinkelmann *et al.* 2013; Steudte *et al.* 2013; Steudte-

Schmiedgen *et al.* 2015)—a finding also being confirmed in the presented data.

There are some important limitations of this study. First, the sample was restricted to male military personnel. Thus, the generalizability of the suggested findings might be limited. Besides missing information for women, PTSD symptoms were relatively low given the considerable trauma exposure. This indicates a high proportion of resilient individuals which has been observed for the German military in general (Trautmann *et al.* 2016). Hence, future studies should replicate the presented findings in more unselected populations. Second, it was not feasible to predict the development of clinically important categories such as binge drinking, heavy use or substance use disorders because of the restricted sample size and the relatively low prevalence of these conditions in the examined population (Trautmann *et al.* 2014). Thus, the clinical implications of our novel findings have still to be determined. Third, the relationship between traumatic event exposure and alcohol misuse is known to be moderated by genetic factors (e.g. Copeland *et al.* 2011) that could not be considered in this study. Fourth, we considered the number rather than exposure to specific events that neglects a potential role of type and timing of events. Finally, there are other potential biological indicators of stress (e.g. corticotropin releasing hormone, adrenocorticotropic hormone and cortisol awakening response) that might also be useful makers for the risk of increased alcohol use following traumatic events (Junghanns *et al.* 2007; Schäfer *et al.* 2010). Moreover, future investigations should combine hair cortisol analysis with further methods to asses HPA axis function, such as pharmacological challenge tasks (e.g. dexamethasone suppression test and dexamethasone-corticotropin-releasing hormone challenge test) or *in vitro* assessments of glucocorticoid receptor number and function in mononuclear leukocytes (De Kloet *et al.* 2006; van Zuiden *et al.* 2012b) in order to ultimately understand the complex relationships between different aspects of HPA axis activity and their role for developing alcohol misuse following traumatic events.

In summary, we provide first evidence that basal cortisol levels as measured by HCC might be a valid biological risk marker for the identification of individuals vulnerable for increased alcohol use after trauma exposure. Future studies should further explore the value of this marker to allow targeted preventive measures that could reduce the risk of alcohol misuse and its adverse consequences.

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DISCLOSURE/CONFLICT OF INTEREST

All other authors declare that they have no conflict of interests.

Authors Contribution

ST wrote the manuscript and conducted the statistical analyses. MM and TS contributed substantially to the interpretation of the data. CK and HUW were principal investigators and responsible for conception and design of the study program. MH supervised the statistical analyses and contributed substantially to the interpretation of the data. SSS was responsible for the sample collection and laboratory analyses of biological markers of stress and contributed substantially to the interpretation of the data. All co-authors revised the manuscript for important intellectual content.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 and Table S2

7 Biological stress indicators as risk markers for PTSD symptoms following traumatic experiences.

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Hair cortisol concentrations and cortisol stress reactivity predict PTSD symptom increase after trauma exposure during military deployment

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Summary
Background: Previous evidence on endocrine risk markers for posttraumatic stress disorder (PTSD) has been inconclusive. Here, we report results of the first prospective study to investigate whether long-term hair cortisol levels and experimentally-induced cortisol stress reactivity are predictive of the development of PTSD symptomatology in response to trauma during military deployment.
Methods: Male soldiers were examined before deployment to Afghanistan and at a 12-month post-deployment follow-up using dimensional measures for psychopathological symptoms. The predictive value of baseline (i) hair cortisol concentrations (HCC, $N = 90$) and (ii) salivary cortisol stress reactivity (measured by the Trier Social Stress Test, $N = 80$) for the development of PTSD symptomatology after being exposed to new-onset traumatic events was analyzed.
Results: Baseline cortisol activity significantly predicted PTSD symptom change from baseline to follow-up upon trauma exposure. Specifically, our results consistently revealed that lower HCC and lower cortisol stress reactivity were predictive of a greater increase in PTSD symptomatology in soldiers who had experienced new-onset traumatic events (explaining 5% and 10.3%

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of variance, respectively). Longitudinal analyses revealed an increase in HCC from baseline to follow-up and a trend for a negative relationship between HCC changes and the number of new-onset traumatic events. Additional pre-deployment analyses revealed that trauma history was reflected in lower HCC (at trend level) and that HCC were negatively related to stressful load.
Conclusions: Our data indicate that attenuated cortisol secretion is a risk marker for subsequent development of PTSD symptomatology upon trauma exposure. Future studies are needed to confirm our findings in other samples.

1. Introduction

While epidemiological studies suggest that 41—86% of all people experience at least one traumatic event during their lifetime, only a relative minority (<10%) of these individuals actually develops posttraumatic stress disorder (PTSD; e.g., Breslau, 2009; Lukaschek et al., 2013; Wittchen et al., 2012a, 2013). This fact has prompted a substantial effort to identify biological vulnerability factors for PTSD with a particular focus on the regulation of neuroendocrine stress systems (reviewed in Bomyea et al., 2012; Zoladz and Diamond, 2013).

Previous *cross-sectional* research suggests that PTSD is related to a complex dysregulation of the hypothalamic—pituitary—adrenal (HPA) axis and its end product cortisol. Regarding basal cortisol secretion, most but not all studies have indicated general hypocortisolism in PTSD patients (for meta-analyses see Meewisse et al., 2007; Morris et al., 2012). Research on cortisol stress reactivity has also revealed mixed results: while some studies found PTSD patients to exhibit an exaggerated cortisol response to a variety of acute stressors (e.g., Bremner et al., 2003; Elzinga et al., 2003), others have failed to replicate this association (e.g., Simeon et al., 2007). In addition to studies suggesting cortisol dysfunctions specifically related to PTSD, growing evidence indicates that trauma exposure per se might be related to altered cortisol secretion. Specifically, it has been shown that traumatized healthy individuals also exhibit lower basal cortisol levels (for a meta-analysis see Morris et al., 2012) and diminished cortisol stress reactivity to psychosocial stress (e.g., Elzinga et al., 2008; Lovallo et al., 2012).

So far it remains unclear whether a dysregulation of cortisol production in PTSD patients either represent a premorbid vulnerability factor or reflect a response to trauma exposure. Interestingly, prospective research suggests that lower basal cortisol levels immediately after a traumatic event predict a higher risk for developing PTSD symptoms (e.g., Delahanty et al., 2000; Mouthaan et al., 2014) and that prior traumatization may underlie this association (e.g., Delahanty et al., 2003; Walsh et al., 2013). However, as these studies measured cortisol levels immediately after trauma exposure, it is unclear whether observed effects can be attributed to peri-traumatic conditions (cortisol response to the traumatic event) or result from pre-traumatic differences in cortisol secretion. The few truly prospective studies which have investigated basal cortisol levels *before* trauma exposure among high-risk groups have failed to demonstrate a predictive value of cortisol levels for PTSD symptomatology at follow-up (e.g., Heinrichs et al., 2005; van Zuiden et al., 2011b, 2012a). However, some studies found that a higher pre-traumatic number of glucocorticoid receptors (GRs; van Zuiden et al., 2011a, 2012a) and increased glucocorticoid (GC) sensitivity (van Zuiden et al., 2012b) predicted PTSD symptom development after military deployment. As it has been proposed that these vulnerabilities in glucocorticoid-signaling are associated with hypocortisolism (e.g., Rohleder et al., 2004; Yehuda et al., 1991), these studies provide indirect evidence for the notion of a predictive value of lower cortisol activity for PTSD symptom development.

An important limitation of the above studies is that previous cortisol assessment strategies in blood, saliva, or urine particularly only provide a reflection of short-term hormone levels (reviewed in Stalder and Kirschbaum, 2012). Hair cortisol analysis is likely to fill this methodological gap as it serves as a valid and reliable index of *long-term integrated* cortisol secretion (Stalder and Kirschbaum, 2012; Staufenbiel et al., 2013). Importantly, growing evidence highlights the potential of hair cortisol concentrations (HCC) as a correlate of long-term PTSD and trauma-related cortisol aberrations (Luo et al., 2012; Steudte et al., 2013; Steudte et al., 2011). Moreover, recent work by our laboratory showed that temporally distant trauma exposure is reflected in lower HCC in both PTSD patients *and* healthy controls, and that a large number and frequency of traumatization is related to lower HCC (Steudte et al., 2013). While this finding matches well with the above studies suggesting that prior traumatization is related to lower cortisol levels immediately after a subsequent traumatic event and a higher risk for developing PTSD, the cross-sectional nature of this study prevented direct testing of this hypothesis.

Given the unique potential of HCC to reflect *retrospective* information, Luo et al. (2012) obtained hair strands of adolescent survivors of the Wenchuan earthquake in China seven months after the disaster. Their findings revealed increased HCC in trauma-exposed individuals (with and without PTSD) in hair segments reflecting the period immediately after trauma exposure which were found to decline in PTSD patients in hair segments reflecting later time periods after trauma exposure (two to seven months). Importantly, no group differences in cortisol levels in the hair segment grown *before* the earthquake were detected. In this context, however, it is important to note that previous research suggests a declining pattern of HCC from proximal to more distal hair segments (''wash-out'' effect, reviewed in Stalder and Kirschbaum, 2012). Considering that Luo et al. (2012) took hair samples seven months after trauma exposure, it is conceivable that this may have weakened the possibility to detect existing associations. Thus, the current

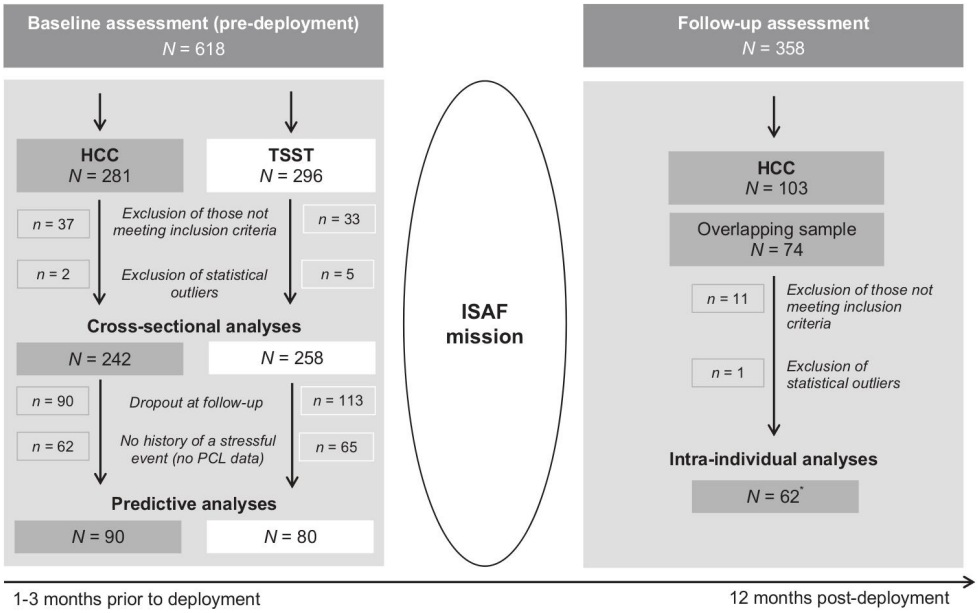

Figure 1 Design and sampling procedure of the prospective study. *Abbreviations*: HCC = hair cortisol concentrations; ISAF = German International Security Assistance Force; PCL = Posttraumatic Stress Disorder Checklist; TSST = Trier Social Stress Test. * $n = 34$ reported the experience of at least one lifetime stressful event (i.e., filled in the PCL).

study obtained hair samples *before* trauma exposure to more closely investigate the role of pre-traumatic HCC as a risk factor for the development of PTSD symptoms. Further, to our knowledge, no prospective studies have been reported that examined the predictive value of cortisol stress reactivity for developing PTSD symptoms.

This study *prospectively* examined soldiers before and on average 12 months after military deployment to Afghanistan (described in Wittchen et al., 2012b). We analyzed the predictive value of baseline (i) long-term HCC and (ii) experimentally-induced cortisol stress reactivity for the development of PTSD symptomatology. Given that the number of traumatic events is known to crucially influence PTSD symptom development (e.g., Neuner et al., 2004) together with our previous evidence of cortisol relationships with traumatic load (Steudte et al., 2011; 2013), we additionally examined whether pre-deployment cortisol secretion and the number of new-onset traumatic events *interactively* predicted PTSD symptom increase. Besides predictive analyses, we investigated whether the number of new-onset traumatic events and PTSD symptom change relate to intra-individual changes in HCC from baseline to follow-up. Finally, given our recent finding indicating that trauma history is a correlate of long-term cortisol attenuation (Steudte et al., 2013) we examined whether the experience of at least one lifetime traumatic event is associated with altered cortisol activity before military deployment.

2. Materials and methods

2.1. Participants

The current project is part of the prospective-longitudinal component of the Prevalence, Incidence and Determinants of PTSD and Other Mental Disorders (PID-PTSD^{+3}) study examining deployment-related disorders in the German federal defense force. Detailed information on the design and methods is provided in Wittchen et al. (2012b). Briefly, male soldiers ($N = 618$) were examined 1—3 months before deployment to Afghanistan (baseline) as part of the German International Security Assistance Force (ISAF) mission in 2011/2012 and on average 12 months after their return (follow-up, $N = 358$, see Fig. 1). There was no evidence for selective dropout from baseline to follow-up in the overall sample (see Trautmann et al., 2015).

In the total sample mean deployment duration was 5.17 months (SD 1.45). At both measurement points, participants were interviewed using the military version of the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI; Wittchen and Pfister, 1997), a fully standardized diagnostic instrument for the assessment of symptoms, syndromes and diagnoses of DSM-IV-TR mental disorders. The current study focused on dimensional measures for psychopathological symptoms which were supplemented to the DIA-X/M-CIDI. In particular, PTSD symptomatology was assessed by the PTSD Checklist (PCL, Weathers et al., 1997) in soldiers who had reported the experience of at least one stressful event in the CIDI-PTSD module (see below). Hair strands were obtained from 281 soldiers at baseline and restricted to participants who had a hair length of at least 2 cm at the posterior vertex region of the scalp and showed no signs of hair loss or baldness. Further, 296 soldiers of the initial sample participated in the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) only once at baseline. Assignment to the TSST was random due to logistical restrictions (availability of the assessment rooms). At follow-up due to attrition we were able to repeatedly collect hair samples from 103 soldiers with hair samples being available for both assessments for 74 soldiers (see Fig. 1).

Table 1 Baseline demographic, hair-related and military characteristics.

	HCC sample ($N = 90^{\dagger}$)	TSST sample ($N = 80^{\dagger}$)	p^{*}
Demographics			
Age, year (M, SD)	27.68 (6.11)	27.78 (5.86)	.963
Body mass index (M, SD)	25.45 (2.69)	25.35 (2.56)	.753
Smoking (%)	51 (56.7)	46 (57.5)	.778
Alcohol consumption in the previous year			.488
Never/rare (%)	11 (12.2)	13 (16.3)	
Occasional (%)	66 (73.3)	57 (71.3)	
Regular (%)	5 (5.6)	4 (5.0)	
Harmful (%)	8 (8.9)	6 (7.5)	
Physical diseases (%)	37 (41.1)	35 (43.8)	.686
Allergy (%)	27 (30.0)	23 (28.7)	
High blood pressure (%)	4 (4.4)	8 (10)	
Asthma (%)	5 (5.6)	5 (6.3)	
Thyroid diseases (%)	4 (4.4)	1 (1.3)	
Medication intake within the last 30 days (%)	36 (41.4)	32 (41.6)	.834
Military characteristics			
Rank[a]			.973
Lower ranks (%)	30 (33.7)	26 (32.9)	
Intermediate ranks (%)	49 (55.1)	44 (55.7)	
Higher ranks (Officer, %)	10 (11.2)	9 (11.4)	
Unit[a]			.437
Combat (%)	45 (50.6)	34 (43.0)	
Medical (%)	7 (7.9)	6 (7.6)	
Other (%)	37 (41.6)	39 (49.4)	
At least one previous deployment (%)	42 (46.7)	33 (41.3)	.370
Number of previous deployments (M, SD)	1.20 (1.82)	1.01 (1.65)	.215
Hair-related variables			
Washes per week (M, SD)[b]	6.13 (2.02)	N/A	
Curls/waves (%)[c]	14 (15.6)	N/A	
Hair treatment (%)[b]	4 (4.4)	N/A	

Abbreviations: HCC = hair cortisol concentrations; TSST = Trier Social Stress Test.
[a] Values refer to $N = 89$ (HCC sample) and $N = 79$ (TSST sample).
[b] Value refers to $N = 79$.
[c] Value refers to $N = 80$.
[†] Overlapping sample: $n = 47$.
[*] P-values refer to the comparison of the non-overlapping samples (HCC sample: $n = 43$, TSST sample: $n = 33$).

General exclusion criteria for the endocrine measures were any severe physical disease (e.g., cancer, adrenocortical dysfunction, neurological diseases) over the past 5 years, and/or use of psychotropic medications (e.g., antidepressants) within the past 6 months (based on self-report). Further, participants with a lifetime diagnosis of substance dependence, psychosis or bipolar disorder either at baseline or follow-up were excluded. This resulted in a total sample of 244 participants providing hair samples at baseline with full PCL data sets being available for predictive analyses from $N = 91$. The final sample for cortisol stress reactivity consisted of 263 participants at baseline with full PCL data sets being available for predictive analyses from $N = 81$. For longitudinal HCC analyses, full PCL data sets were available for 34 out of 63 participants (see Fig. 1). Table 1 provides descriptive information on baseline demographic, hair-related and military characteristics of soldiers included in the predictive HCC and TSST analysis. Data for both cortisol measures were available for 47 soldiers. Importantly, no differences in demographic and military characteristics were observed between the non-overlapping samples ($ps > .215$, see Table 1). Further, no differences were seen between predictive samples and the overall baseline sample, except for a higher probability to be enlisted in higher ranks for soldiers included in the predictive HCC and TSST analysis, respectively ($ps < .01$).

All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Technische Universität Dresden Medical School (EK 72022010).

2.2. Clinical and psychological measures

The respondent-booklets of the DIA-X/M-CIDI were supplemented with interviewer and self-reported questions and modules relevant for the study aims and the military

context. Among others, information on sociodemographic variables (sex, age, smoking status, body mass index, alcohol consumption), hair-specific characteristics (washes per week, curls/waves, hair treatments) and participants' health (medication intake, physical diseases) were obtained. As part of the CIDI-PTSD module we assessed for all participants both the number of ''stressful'' (A1 criteria of DSM-IV for PTSD) and the number of qualifying ''traumatic'' (A1 *and* A2 criteria of DSM-IV for PTSD) events. In addition, the MHAT-IV list (Wittchen and Schönfeld, 2009) was incorporated to assess the number and frequency of combat-related experiences. The PCL (Weathers et al., 1997) was used to measure the severity of overall PTSD symptoms with sum scores ranging from 17 to 85, including the three subscales reflecting DSM-IV-TR cluster criteria for PTSD (intrusions, avoidance, hyperarousal). The severity of maltreatment in childhood was measured by the Childhood Trauma Questionnaire (CTQ, Wingenfeld et al., 2010). Additionally, the revised CIDI-Depression Screening Questionnaire (DSQ-34, Wittchen and Schönfeld, 2009) was used to assess the severity of depressiveness over the last week.

2.3. Sample collection and preparation

2.3.1. Hair cortisol analysis

Hair strands (~3 mm diameter) were taken scalp-near from a posterior vertex position. HCC in the proximal 2-cm hair segment were measured reflecting integrated cortisol secretion over the 2 month-period prior to hair sampling (reviewed in Stalder and Kirschbaum, 2012). HCC were determined via liquid chromatography tandem mass spectrometry. Detailed information on the analytical protocol is provided in Gao et al. (2013).

2.3.2. Cortisol stress reactivity

The Trier Social Stress Test (TSST; Kirschbaum et al., 1993) is an effective standardized protocol for the reliable induction of acute psychosocial stress under laboratory conditions (reviewed in Allen et al., 2014; Foley and Kirschbaum, 2010). A detailed description of the experimental procedure is provided in Wittchen et al. (2012b). In brief, the TSST consists of a public speaking (5 min) and a mental arithmetic task (5 min) performed in front of two evaluating panelists. Participants were instructed to refrain from smoking, eating and drinking anything but water 60 min prior to the TSST. Saliva samples were collected immediately before the TSST as well as 1, 10 and 20 minutes after the TSST using Salivette devices (Sarstedt, Rommelsdorf, Germany). Samples were stored at −20 °C in a laboratory freezer. After thawing, saliva samples were centrifuged for 10 min at 4000 rpm. Salivary cortisol concentrations were analyzed using a commercially available luminescence assay (LIA, IBL-Hamburg, Germany).

2.4. Data exclusion and statistical analysis

Analyses were performed using SPSS for Windows, version 22 (IBM, Chicago, Illinois). Hair cortisol and salivary cortisol data were not normally distributed, thus log transformations were applied to reduce skewness statistics. Changes in clinical characteristics from baseline to follow-up were examined by using repeated measures analysis of covariance (ANCOVA) with baseline values as covariate. Group comparisons in sociodemographic and hair-related characteristics between soldiers who had experienced at least one lifetime traumatic event before deployment and non-traumatized soldiers were conducted using t-tests (continuous variables) and Fisher's exact tests (dichotomous variables). In case of significant group differences, these variables were subsequently included as covariates.

For HCC analyses, data from three participants were excluded due to outlying values of more than three standard deviations above the mean (see Fig. 1). A one-way ANOVA was carried out to examine the impact of the experience of at least one lifetime traumatic event on HCC before deployment. Spearman correlations were further applied to examine HCC relationships with the number of stressful and traumatic events as well as CTQ scores. A stepwise regression analysis with PCL change scores as dependent variable and initial PCL scores, baseline HCC and the number of new-onset and baseline traumatic events as independent variables was conducted. As a second step, the interaction term between baseline HCC × number of new-onset traumatic events was entered in the model to examine the predictive value of HCC for the development of PTSD symptoms as a function of trauma exposure. F-tests were used to test whether the inclusion of the interaction term contributed to a significant increase in the amount of explained variance. Due to multicollinearity issues isolated test statistics are not interpretable. To investigate associations between intra-individual changes in HCC and PCL scores as well as in the number of traumatic events, change scores were computed for respective variables by subtracting baseline from follow-up values. Relationships between these scores were then examined by using partial correlational analyses, controlling for respective baseline values. Further, HCC changes from baseline to follow-up were analyzed by conducting repeated measures ANCOVA with baseline HCC values as covariate.

For cortisol stress reactivity, data from five participants were excluded due to outlying values of more than three standard deviations above the mean (see Fig. 1). Salivary cortisol data were analyzed by repeated measures ANCOVA with baseline cortisol values as covariate across the complete sample. To test for the influence of the experience of at least one lifetime traumatic event on cortisol stress reactivity before deployment a two-way repeated measures ANCOVA with measurement time [4] as within-subject factor and group [2] as between-subject factor with baseline cortisol values as covariate was conducted. The area under the curve with respect to increase (AUC_I) was calculated as a composite measure reflecting the cortisol stress response to the TSST (Pruessner et al., 2003). Spearman correlations were conducted to examine relationships between AUC_I salivary cortisol and the number of stressful and traumatic events as well as CTQ scores. As described for HCC, a stepwise regression analysis was conducted, examining the predictive value of AUC_I salivary cortisol together with initial PCL scores, the number of new-onset and baseline traumatic events for PCL change scores from baseline to follow-up. Again, it was examined whether the inclusion of the AUC_I × number of new-onset traumatic event interaction (model 2) resulted in a significant increase in the amount of

Table 2 Trauma-related and psychological characteristics at baseline and follow-up.

	HCC sample ($N = 90$)			TSST sample ($N = 80$)		
	Baseline	Follow-up	p^*	Baseline	Follow-up	p^*
Trauma-related characteristics						
Number of stressful events (M, SD)	2.91 (2.10)	4.57 (2.97)	<.001	2.64 (1.98)	4.20 (2.64)	<.001
Number of traumatic events (M, SD)	1.27 (1.27)	1.71 (1.74)	.066	1.23 (1.29)	1.74 (1.72)	<.01
Number of different combat experiences (M, SD)	7.07 (7.02)[a]	9.47 (6.64)[a]	<.001	5.97 (5.48)[b]	8.34 (5.98)[b]	<.01
Frequency of combat experiences (M, SD)	27.33 (27.76)[a]	40.13 (36.91)[a]	<.01	22.63 (24.80)[b]	31.20 (23.86)[b]	<.001
Psychological characteristics						
PCL score (M, SD)	19.63 (4.11)	20.06 (6.43)	.039	19.19 (4.13)	19.66 (5.86)	.015
Intrusion (M, SD)	5.73 (1.31)	5.74 (1.90)	<.001	5.55 (1.14)	5.79 (1.95)	<.01
Avoidance (M, SD)	7.88 (1.55)	7.96 (2.14)	.013	6.70 (1.42)	6.61 (1.69)	<.001
Hyperarousal (M, SD)	5.90 (2.27)	6.14 (2.81)	<.001	5.88 (2.38)	6.15 (2.58)	<.001
DSQ-34 score (M, SD)	8.73 (7.66)	9.10 (9.26)	<.01	8.40 (7.38)	8.68 (9.44)	.027
CTQ score (M, SD)	31.53 (7.44)[c]	N/A		31.61 (6.86)[d]	N/A	

Abbreviations: CTQ = Childhood Trauma Questionnaire; DSQ-34 = revised CIDI-Depression Screening Questionnaire; HCC = hair cortisol concentrations; PCL = Posttraumatic Stress Disorder Checklist; TSST = Trier Social Stress Test.

[a] Value refers to $N = 45$.

[b] Value refers to $N = 35$.

[c] Value refers to $N = 89$.

[d] Value refers to $N = 79$.

[*] p-Values refer to the repeated measures ANCOVA with baseline values as covariate.

explained variance. Finally, Pearson correlational analysis was conducted to examine the relationship between AUC_I salivary cortisol and HCC.

3. Results

3.1. Sample characteristics and cross-sectional baseline associations

Table 2 summarizes the clinical characteristics for participants included in the predictive HCC ($N = 90$) and TSST analysis ($N = 80$) at baseline and follow-up. The number of experienced stressful ($ps < .001$) and traumatic events ($ps < .066$) as well as the frequency and number of combat experiences ($ps < .01$) reported were found to increase over time. At follow-up, 73.3% of the HCC sample and 77.3% of the TSST sample reported the experience of at least one new-onset *stressful* event while 26.7% of the HCC sample and 27.3% of the TSST sample reported at least one new-onset *traumatic* event. The mean level of PTSD symptomatology and depressiveness increased from baseline to follow-up ($ps < .039$).

Baseline comparisons revealed no differences in sociodemographic and hair-related characteristics between soldiers who had experienced at least one lifetime traumatic event before deployment and non-traumatized soldiers ($ps > .11$; $N = 242$), except for an older age ($t_{199.761} = -2.436$, $p = .016$) and marginally higher BMI ($t_{240} = -1.904$, $p = .058$) in the traumatized group. An ANCOVA controlling for age and BMI revealed a non-significant trend for lower HCC in traumatized compared to non-traumatized soldiers ($F_{1,\ 238} = 2.764$, $p = .098$, $\eta_p^2 = .011$, see Table 3). In addition, a negative HCC association with the number of different lifetime stressful events ($r_s = -.142$ $p = .028$), but not with traumatic events ($r_s = -.081$, $p = .208$) or CTQ scores ($r_s = -.006$, $p = .925$) was seen. Salivary cortisol levels were found to increase in response to the TSST across the complete baseline sample ($F_{1.995,\ 510.794} = 108.395$, $p < .001$, $\eta^2 = .297$, $N = 258$). An ANCOVA controlling for baseline cortisol values, age and BMI revealed no influence of trauma history on cortisol stress reactivity ($F_{1.992,\ 503.887} = .145$, $p = .864$, $\eta^2 = .001$, see Table 3). AUC_I salivary cortisol was unrelated to the number of different lifetime stressful or traumatic events or CTQ scores ($ps > .649$).

3.2. Predictive analyses

Table 4 shows results of stepwise regression analysis examining the predictive value of PTSD symptomatology, number of baseline traumatic events, new-onset traumatic events and baseline (a) HCC ($N = 90$) as well as (b) cortisol stress reactivity ($N = 80$) for the change in PTSD symptoms from baseline to follow-up.

3.2.1. Hair cortisol

Findings revealed a negative effect of initial PTSD symptomatology ($\Delta R^2 = .043$, $F_{1,88} = 3.96$, $p = .050$), a positive association with the number of new-onset traumatic events ($\Delta R^2 = .378$, $F_{1,87} = 56.71$, $p < .001$), and no effect of baseline number of traumatic events ($\Delta R^2 = .003$, $F_{1,86} = .418$,

Table 3 Comparison of baseline HCC and salivary cortisol in response to the TSST in traumatized and non-traumatized soldiers.

	Traumatized soldiers	Non-traumatized soldiers	*p*
HCC in pg/mg (M, SD)[a]	3.56 (5.03)	4.25 (5.26)	.098[*]
Salivary cortisol in nmol/l (M, SD)[b]			.864[†]
−1 min before TSST	10.58 (5.09)	10.18 (5.27)	
+1 min after TSST	17.92 (9.61)	17.05 (8.56)	
+10 min after TSST	25.41 (12.53)	24.27 (11.67)	
+20 min after TSST	23.81 (11.88)	23.01 (11.48)	

Abbreviations: HCC = hair cortisol concentrations; TSST = Trier Social Stress Test.
[a] $N = 242$ (traumatized: $n = 113$, non-traumatized: $n = 129$).
[b] $N = 258$ (traumatized: $n = 110$, non-traumatized: $n = 148$).
[*] *p*-Value refers to the ANCOVA with age and BMI as covariates.
[†] *P*-Value refers to the repeated measures ANCOVA with baseline values, age and BMI as covariates.

$p = .520$). A non-significant trend for a main effect of baseline HCC ($\Delta R^2 = .021$, $F_{1,85} = 3.14$, $p = .080$) was revealed without accounting for trauma exposure. Importantly, the interaction between baseline HCC × number of new-onset traumatization (model 2) contributed to an additional explanation of 10.3% of variance ($\Delta R^2 = .103$, $F_{1,84} = 19.06$, $p < .001$, see Table 4a). Specifically, lower baseline HCC predicted a rise in PTSD symptomatology in soldiers who had experienced new-onset traumatic events. Fig. 2a further shows this relationship by using dichotomized data (for illustrative purposes only). Including CTQ scores as an additional predictor in the stepwise regression did not change the current main results ($\Delta R^2 = .001$, $F_{1,82} = .19$, $p = .662$).

Table 4 Stepwise regression predicting baseline to follow-up change in PTSD symptoms from initial PTSD symptomatology, number of baseline traumatic events, new-onset traumatic events and baseline (a) HCC ($N = 90$) as well as (b) cortisol stress reactivity ($N = 80$).

Dependent	*F*	Predictor	*B*	SE	Beta	*p*	R^2 adj.
(a) HCC							
PCL change scores	16.974	Model 1:				<.001	.418
		Baseline PCL score	−.424	.121	−.297	<.01	
		Number of baseline traumatic events	−.308	.389	−.067	.430	
		Number of new-onset traumatic events	3.836	.493	.651	<0.001	
		Baseline HCC	−3.636	2.051	−.146	.080	
PCL change scores	20.278	Model 2:				<.001	.520
		Baseline PCL score	−.411	.110	−.288	<.001	
		Number of baseline traumatic events	−.033	.359	−.007	.926	
		Number of new-onset traumatic events	9.374	1.345	1.590	<.001	
		Baseline HCC	2.527	2.337	.101	.283	
		Number of new-onset traumatic events × baseline HCC	−9.414	2.156	−1.065	<.001	
(b) Cortisol stress reactivity (TSST)							
PCL change scores	13.637	Model 1:				<.001	.390
		Baseline PCL score	−.391	.116	−.301	<.01	
		Number of baseline traumatic events	.820	.368	.198	.029	
		Number of new-onset traumatic events	2.751	.440	.554	<.001	
		Baseline AUC_I	−2.508	2.783	−.081	.370	
PCL change scores	13.166	Model 2:				<0.001	.435
		Baseline PCL score	−.394	.111	−.304	<.01	
		Number of baseline traumatic events	.702	.357	.169	.053	
		Number of new-onset traumatic events	23.478	7.872	4.723	<0.01	
		Baseline AUC_I	−.103	2.830	−.003	.971	
		Number of new-onset traumatic events × baseline AUC_I	−.7.451	2.826	−4.183	.010	

Model 1 compared to model 2: (a) $F_{1,84} = 19.064$, $p < .001$; (b) $F_{1,74} = 6.952$, $p = .010$. Abbreviations: AUC_I = area under the curve with respect to increase; HCC = hair cortisol concentrations; PCL = Posttraumatic Stress Disorder Checklist; PTSD = posttraumatic stress disorder; TSST = Trier Social Stress Test.

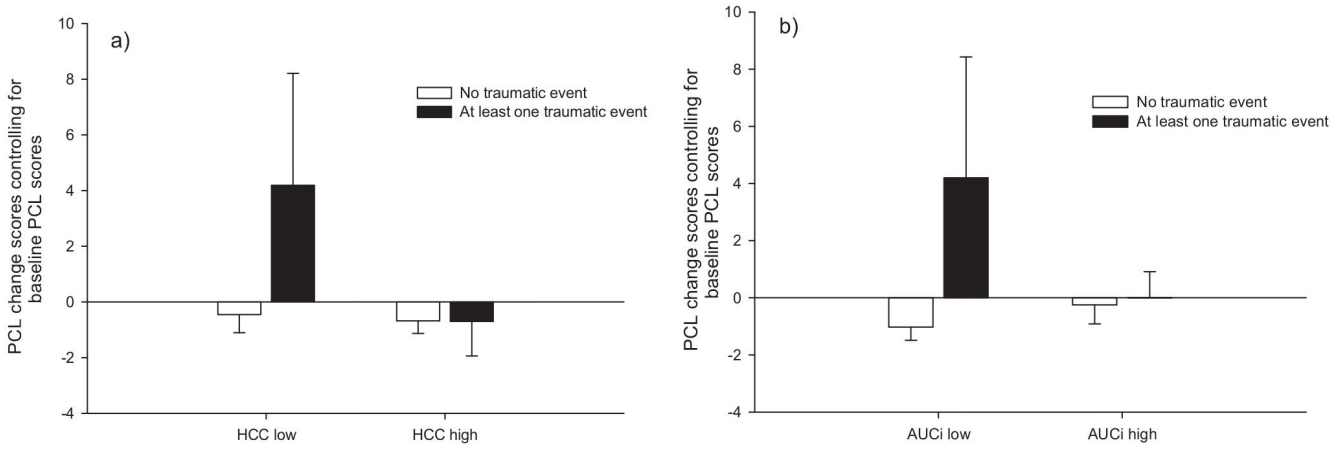

Figure 2 Interaction of new-onset traumatization and baseline (a) HCC ($N = 90$) and (b) cortisol stress reactivity (AUC_I, $N = 80$) for predicting the mean (±SEM) change of PTSD symptomatology from baseline to follow-up controlling for baseline PTSD symptom severity. *Abbreviations*: AUC_I = area under the curve with respect to increase; HCC = hair cortisol concentrations; PCL = Posttraumatic Stress Disorder Checklist.

3.2.2. Cortisol stress reactivity

Consistent with the pattern of HCC findings, a negative effect of initial PTSD symptomatology ($\Delta R^2 = .067$, $F_{1,78} = 5.65$, $p = .020$) and a positive effect of the number of new-onset traumatic events ($\Delta R^2 = .305$, $F_{1,77} = 37.47$, $p < .001$) on PTSD symptom change was found. There was a positive effect of the baseline number of traumatic experiences ($\Delta R^2 = .042$, $F_{1,76} = 5.46$, $p = .022$), but no effect of AUC_I salivary cortisol ($\Delta R^2 = .006$, $F_{1,75} = .812$, $p = .370$). Again, the inclusion of the interaction term of baseline $AUC_I \times$ number of new-onset traumatic events (model 2) contributed an additional 5% explanation of variance ($\Delta R^2 = .050$, $F_{1,74} = 6.95$, $p = .010$, see Table 4b). Specifically, lower salivary cortisol AUC_I predicted a rise in PTSD symptomatology in soldiers who had experienced new-onset traumatic events. Fig. 2b illustrates this relationship by using dichotomized data. Including CTQ scores as an additional predictor in the stepwise regression did not change the current main results ($\Delta R^2 = .000$, $F_{1,72} = .04$, $p = .844$). Pearson correlation analysis revealed a trend for a positive relationship between HCC and AUC_I salivary cortisol ($r = .254$, $p = .085$, $N = 47$).

3.3. Longitudinal HCC analyses

Partial correlational analyses examining relationships between intra-individual changes from baseline to follow-up controlling for respective baseline values revealed no significant association between changes in HCC and changes in PCL scores ($r = -.123$, $p = .503$, $N = 34$), but a trend for a negative relationship between changes in HCC and the number of new-onset traumatic events ($r = -.239$, $p = .066$, $N = 62$). A repeated measures ANCOVA revealed that HCC increased from baseline to follow-up across the whole sample ($F_{1,60} = 46.725$, $p < .001$, $\eta^2 = .438$, $N = 62$).

4. Discussion

This prospective study is the first to investigate the predictive value of pre-traumatic long-term cortisol levels in hair and acute cortisol stress reactivity for the development of PTSD symptomatology after exposure to traumatic events in the context of military deployment. Findings consistently revealed that both lower baseline HCC and lower cortisol stress reactivity were predictive of the development of PTSD symptomatology upon trauma exposure. In addition, the current findings tentatively support our previous results showing that trauma exposure per se is associated with attenuated long-term cortisol secretion and that HCC are negatively related to the number of lifetime stressful events.

The main finding of the current study was that baseline endocrine markers (long-term HCC and acute cortisol stress reactivity) were predictive of changes in PTSD symptomatology upon trauma exposure. Specifically, attenuated baseline cortisol activity was predictive of a substantially greater increase of PTSD symptomatology in those soldiers who had experienced new-onset traumatic events (explaining 5% and 10.3% of variance, respectively). Although this is in line with some previous studies suggesting that reduced basal cortisol levels assessed immediately after traumatization may be a risk factor for subsequent development of PTSD (e.g., Delahanty et al., 2003; Walsh et al., 2013), studies assessing cortisol levels before trauma exposure have not been able to confirm this notion (e.g., Heinrichs et al., 2005; van Zuiden et al., 2011b, 2012a). As these studies used spot cortisol markers assessed from plasma and saliva samples without prior stimulation, it is likely that respective results were affected by the acute context of the measurement situation (e.g., Stalder et al., 2010). This seems unlikely for the current HCC findings, which are assumed to reflect cortisol secretion over extended periods of time and are thus unaffected by short-term changes in cortisol secretion (reviewed in Stalder and Kirschbaum, 2012). In addition, given that HCC were analyzed in a scalp-near hair segment obtained *before* deployment, the current study results were not confounded by a potential wash-out effect (as opposed to Luo et al., 2012). A further important difference between the current research and the above prospective studies is that we investigated the predictive value of pre-traumatic cortisol activity for PTSD symptom increase as a function of

trauma exposure. Specifically, the *interaction* between cortisol and the number of new-onset traumatic events was taken into account. The current pattern of findings thus suggests that indices of traumatic load need to be considered by future investigations trying to elucidate the role of pre-traumatic endocrine risk markers for PTSD.

Importantly, the same pattern of predictions was evident for cortisol stress reactivity, which further supports the notion that attenuated cortisol secretion constitutes a risk marker for developing PTSD symptoms upon trauma exposure. Therefore, our findings complement previous research identifying vulnerability factors in other aspects of GC-signaling for the development of PTSD symptomatology, such as a higher number of GRs (van Zuiden et al., 2011a, 2012a) and increased GC sensitivity (van Zuiden et al., 2012b). A proposed mechanism through which diminished cortisol secretion may increase PTSD risk involves the effects of glucocorticoids on PTSD-relevant memory processes. In the aftermath of trauma, attenuated cortisol levels may induce a neuroendocrine environment leading to inadequate consolidation of traumatic memories (reviewed in Yehuda, 2009; Zoladz and Diamond, 2013) and to increased perceptual priming for neutral stimuli in a traumatic context (Holz et al., 2014). Interestingly, it has been suggested that effects of inflammatory disinhibition that may result from low cortisol activity contribute to a higher risk of PTSD development. Here, a recent prospective study (Smid et al., 2015) showed that after high combat stress exposure, high cytokine production was associated with increases in PTSD symptomatology in response to post-deployment stressful life events. It has been proposed that this may be due to detrimental effects of high cytokine production on PTSD-relevant memory processes (Smid et al., 2015; Yirmiya and Goshen, 2011).

Besides predictive analyses, current cross-sectional data seem to be in line with our recent finding (Steudte et al., 2013) suggesting that the experience of at least on lifetime traumatic event is associated with lower HCC (at trend level) as well as a negative HCC relationship with the number of lifetime stressful events. Interestingly, the latter is also commensurate with the current finding of a negative association between indices of new-onset traumatic load and intra-individual changes in HCC from baseline to follow-up (at trend level). These results provide tentative evidence for the notion that exposure to traumatic stress is related to long-term changes in cortisol secretion even in otherwise healthy individuals (see also Morris et al., 2012).

Taken these considerations and our prediction findings together the following two-staged process of endocrine alterations in response to traumatic stress is conceivable: (i) trauma exposure may result in a long-term dose-dependent cortisol attenuation, which, in turn, (ii) may predispose PTSD development upon exposure to additional traumatic events. Moreover, it is important to note that further biological factors have been shown to contribute to attenuated cortisol secretion (e.g., genetic variation) and might thus also mediate the risk of developing PTSD symptoms in response to trauma (reviewed in Bomyea et al., 2012; Kolassa and Elbert, 2007; Zoladz and Diamond, 2013).

Some limitations of the current research should be considered. Due to the restricted power we limited the analyses to a self-report dimensional PTSD measure and did not examine associations with the categorical diagnostic outcome, yet. The sample consisted exclusively of male soldiers deployed to Afghanistan as part of the German ISAF contingent limiting the generalizability of findings. This is also relevant with regard to the fact that the current prediction findings only refer to soldiers who experienced at least one lifetime stressful event. Due to lack of funds, we were unable to measure endocrine markers in a control group of *non-deployed* soldiers. Thus, it is unclear whether the current observation of HCC increase from baseline to follow-up may have resulted from deployment-related stress or rather from other unknown factors. Another potential limitation relates to the fact that the predictive HCC and TSST analyses were conducted on samples that were only partially overlapping which may have led to a slightly different pattern of results. However, importantly, the main finding of lower cortisol activity as a predictor of PTSD symptom increase upon trauma exposure is consistent.

Future research is needed to repeatedly assess HCC during and after deployment to obtain detailed information on the specific timeline of endocrine alterations in response to traumatic stress (see also Miller et al., 2007; Trickett et al., 2010). Given previous evidence suggesting beneficial effects of hydrocortisone administration immediately after trauma exposure for preventing the development of PTSD (reviewed in Hruska et al., 2014), future research should aim to examine whether pre-traumatic cortisol activity might modulate the efficacy of such hydrocortisone treatment.

To conclude, the current findings provide first evidence that lower long-term cortisol secretion and lower cortisol stress reactivity are risk markers for the development of PTSD symptomatology upon trauma exposure. Future prospective studies are needed to confirm the current findings in other samples.

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Conflict of interest statement

All authors have nothing to disclose.

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8 The MAOA gene as moderator of the association between trauma history and outcome of CBT

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ORIGINAL PAPER

Does prior traumatization affect the treatment outcome of CBT for panic disorder? The potential role of the *MAOA* gene and depression symptoms

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Abstract Although cognitive behavioral therapy (CBT) is highly effective in the treatment of anxiety disorders, many patients still do not benefit. This study investigates whether a history of traumatic event experience is negatively associated with outcomes of CBT for panic disorder. The moderating role of the monoamine oxidase A (*MAOA*) gene and depression symptoms as well as the association between trauma history and fear reactivity as a potential mechanism are further analyzed. We conducted a post-hoc analysis of 172 male and 60 female patients with panic disorder treated with CBT in a multi-center study. Treatment outcome was assessed at post-treatment using self-report and clinician rating scales. Fear reactivity before treatment was assessed via heart rate and self-reported anxiety during a behavioral avoidance test. Among females, we did not find any differences in treatment response between traumatized and non-traumatized individuals or any two-way interaction trauma history × *MAOA* genotype. There was a significant three-way interaction trauma history × *MAOA* genotype × depression symptoms on all treatment outcomes indicating that in traumatized female patients carrying the low-activity allele, treatment effect sizes decreased with increasing depression symptoms at baseline. No such

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effects were observed for males. In conclusion, we found no evidence for a differential treatment response in traumatized and non-traumatized individuals. There is preliminary evidence for poorer treatment outcomes in a subgroup of female traumatized individuals carrying the low-active variant of the *MAOA* gene. These patients also report more symptoms of depression symptomatology and exhibit a dampened fear response before treatment which warrants further investigation.

Keywords Panic disorder · CBT · Trauma · MAOA · Fear reactivity · Depression

Introduction

Anxiety disorders are highly prevalent in the general population [1, 2] and associated with substantial individual burden and societal costs [3, 4]. Although anxiety disorders can be effectively treated with psychological interventions [5, 6], a considerable proportion of patients does not benefit from existing treatments or report a return of fear after an initially successful treatment [7, 8]. Arguably, the identification of patient characteristics and associated mechanisms underlying poor treatment outcome is essential to inform the modification of existing interventions for anxiety disorders into a more individualized treatment approach with assigning patients to an optimized therapy protocol depending on specific pre-treatment characteristics.

Previous exposure to traumatic events is not only related to the risk for the development of trauma-related disorders such as post-traumatic stress disorder (PTSD) but also for anxiety and depressive disorders with a higher risk for females compared to males [9–14]. Much less is known about the importance of a trauma history for the treatment response of these disorders. Although traumatic events have been associated with neurobiological and psychological changes that might moderate the response to later treatment of mental disorders [15, 16], empirical data are still limited. There is some evidence that a history of traumatic events, particularly in early life, negatively affects response to pharmacological and standardized psychological treatments for depressive disorders suggesting special need for that subgroup of patients [17–19]. In contrast, only very few studies have addressed the association between previous trauma exposure and treatment response for anxiety disorders. Mixed results were observed for the treatment of social anxiety disorders [20–22]. Whereas one study found detrimental effects of previous exposure to trauma on treatment efficacy [20], two studies did not [21, 22]. Further, two studies found no evidence for a differential response to pharmacological or psychological interventions for panic disorder in traumatized as compared to non-traumatized individuals [23, 24]. In summary, trauma exposure might affect treatment effects in anxiety disorders with, however, existing data being highly inconclusive due to a very small number of published studies with generally small sample sizes. Against this background, the present study aims to investigate the association between trauma history and treatment outcome for anxiety disorders for a large group of patients with panic disorder and agoraphobia being treated with highly standardized exposure-based cognitive behavioral therapy (CBT) in a multicenter trial.

One reason for null findings when looking at the effects of traumatization on treatment of anxiety disorders might be the neglect of additional moderating factors in previous studies, such as genetic disposition. For a broad range of adverse neuropsychological and mental health consequences, evidence suggests that genetic influences moderate the effects of trauma exposure [25–29]. A gene that has been associated with pathological anxiety in general and with panic disorder in particular is the monoamine oxidase A (*MAOA*) gene [30]. *MAOA* is important for the degradation of monoamines, especially norepinephrine and serotonin [31]. A common genetic variation in the *MAOA* gene is a 30-bp variable number of tandem repeat (VNTR) polymorphism in the promoter region with longer alleles (3.5, 4 and 5) being associated with higher transcription rates compared to shorter alleles (2 and 3) [32]. Longer alleles have been shown to be associated with panic disorder, particularly in females [30, 33–35], although findings are not entirely consistent [36]. In accordance with case–control studies, a previous analysis from the MAC study framework, which used the same sample as the present study, demonstrated that females with longer alleles show a poorer treatment response to CBT for panic disorder as well as an altered fear reaction to a fearful situation [37]. Importantly, there is also first evidence that the *MAOA* gene is involved in the risk for mental disorders following traumatic events [38, 39]. Given these findings, we hypothesized that variation in the *MAOA* gene might moderate the association between traumatic experiences and treatment outcome. Since effects of traumatization on treatment outcome were already shown for depressive disorders [17], we also considered a potential role of depression symptoms before treatment. Given the limited sample size and little previous work, the simultaneous consideration of trauma history, *MAOA* gene and depression symptoms (three-way interaction) was laid out as an exploratory analysis.

To further explore possible mechanisms associated with trauma history, we also investigated whether traumatized individuals show altered fear reactivity assessed by self-report and autonomic measures in a fear-provoking standardized behavioral avoidance test.

Methods

Data source

Data were derived from a randomized clinical multi-center trial of 369 patients with panic disorder with agoraphobia according to the DSM-IV-TR diagnostic criteria randomized to one of the two standardized variants of CBT or a wait-list-control group and conducted in eight outpatient study centers. Treatment consisted of 12 sessions of manualized CBT treatment carried out over six weeks, followed by two booster sessions. The original study compared two exposure-based CBT variants: in situ exposures were either accompanied by the therapist ($n = 163$) or planned and evaluated in detail in the therapy room with extensive instructions on how to engage in the in situ exposure exercises without the therapist being present ($n = 138$). For the current analysis, patients of both active conditions were grouped together ($N = 301$) since there were only few significant differences in CBT outcomes of limited effect size [40]. More details on recruitment procedure, inclusion and exclusion criteria and treatment specifics have been described previously [40, 41].

Assessments

The DSM-IV diagnoses of panic disorder/agoraphobia and the experience of lifetime traumatic events according to the DSM-IV A1 criterion of PTSD were assessed by trained psychotherapists using the Composite International Diagnostic Interview (CIDI), a fully standardized computer-assisted diagnostic interview [42]. The diagnoses were subsequently verified by a senior clinician. Outcome measures that are reported in the present study include the Hamilton Anxiety Scale (HAM-A) [43], the Clinical Global Impression Scale—Severity Subscale (CGI) [44], patients self-report measures of the Panic and Agoraphobia Scale (PAS) [45], and the Mobility Inventory (MI) [46] indicating agoraphobic avoidance. Depression symptoms were assessed with the Beck Depression Inventory (BDI-II, German version) [47].

Genotyping

Genetic data were available for 172 female and 60 male patients. All patients were genotyped for the *MAOA* VNTR according to published protocols [32, 37] with minor modifications and grouped into a low-activity (20 females and 19 males) and a high-activity (152 females and 41 males) *MAOA* variant as described previously [37]. The high-activity group consisted of 3.5, 4 and 5 allele males, and 3/3.5, 3/4, 3/5, 3.5/4, 4/4, 4/5 and 5/5 allele females. All other individuals were grouped into the low-activity group (see Supplemental Table 1).

Fear reactivity

Of the patients with available genetic data, 149 female and 57 male patients also participated in a standardized behavioral avoidance test (BAT) before and after treatment consisting of an exposure to a small, dark and locked test chamber. In the present analysis, only the baseline BAT data are considered since these are not confounded with treatment effects. During exposure, patients were placed in the chamber and instructed to stay as long as deemed possible. Patients were instructed to rate the intensity of their experienced fear during exposure on a scale from 1 to 10. The electrocardiogram was measured continuously during the whole procedure from which the mean heart rate during the exposure phase was derived. The BAT procedure is described in greater detail elsewhere [37, 48, 49].

Statistical analyses

Lifetime exposure to traumatic events was coded as a dichotomous variable (yes/no). We did not analyze the number of traumatic events since the small variance in the sample (range 0–4 events; 3.9% of the sample reported more than 2 events) would not allow meaningful analyses. Effect sizes (ES) in therapy outcomes were calculated as mean differences of standardized outcome scores between pre- and post-treatment, each divided by the pooled pre-treatment standard deviation. The last observation carried forward (LOCF) method was applied in cases of missing data to increase the available sample. Thus, outcome estimates can be considered as conservative. The dropout rate was 17.1% for the total sample and 15.1% for the subsample with available genetic and BAT data. Tests for selective dropout revealed no association ($p > 0.05$) between dropout and sex, trauma history, *MAOA* genotype, baseline depression and severity of anxiety symptoms (as measured by CGI, PAS and MI) except for a higher baseline HAM-A score in dropouts [OR = 1.3 (95% CI 1.01–1.7) $p = 0.041$ for z-standardized HAM-A score]. Associations between trauma exposure and baseline severity, therapy outcome and fear reactivity, respectively, were investigated using linear regressions. For the analysis of interactions between previous trauma exposure × *MAOA* genotype (high vs. low-activity) × depression symptoms (BDI score) at baseline, separate models were fitted that added the main effect term of the traumatic event variable and the interaction term with the respective moderator (two-way and three-way interactions). We also conducted all analyses including *MAOA* genotype separately

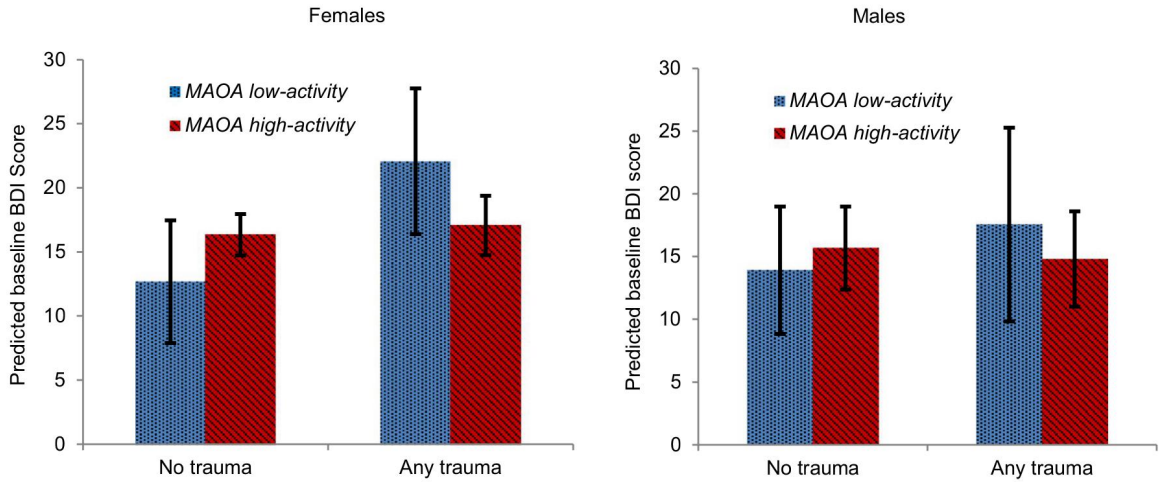


Fig. 1 Interaction trauma experience × *MAOA* gene predicting baseline depression symptoms by gender. *BDI* Beck Depression Inventory, *MAOA* monoamine oxidase A. *Error bars* indicate 95% confidence intervals. Two-way interaction among females is statistically significant ($p < 0.05$)

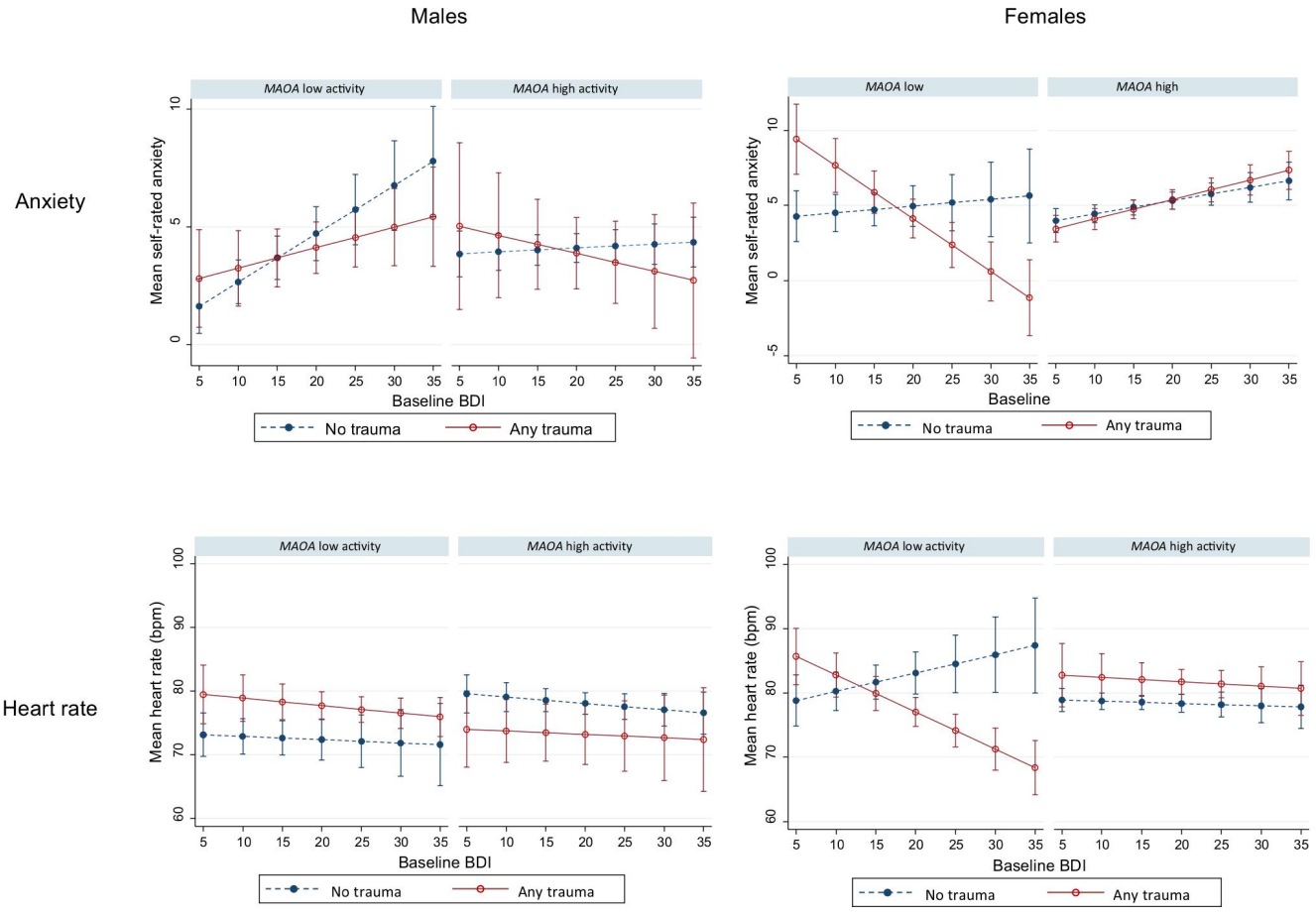


Fig. 2 Interaction trauma experience × *MAOA* gene × baseline depression symptoms predicting fear reactivity in a behavioral avoidance test before treatment by gender. *MAOA* monoamine oxidase A, *BDI* Beck Depression Inventory. *Error bars* indicate 95% confidence intervals. All three-way interactions among females are statistically significant ($p < 0.05$)

for males and females since previous studies suggest sex differences in the effect of *MAOA* genotype on treatment outcomes [30, 37]. Results for the total sample are reported in the online supplement (Supplemental Tables 2 and 3). All regression models with treatment outcome as dependent variable were adjusted for the baseline value of the respective outcome and the treatment condition of the original study design (accompanied vs. not accompanied by the therapist) in a first model and additionally for the potential confounding effect of a PTSD diagnosis ($n = 8$ cases with PTSD) in a second model. Statistical inference was based on the robust Huber–White–sandwich estimator of standard errors [50] because this revealed considerably different results compared to the conventional model-based estimation of standard errors indicating that the robust method should be preferred. Statistical significance was evaluated at the two-sided 5% level. Since we considered multiple outcomes to test one hypothesis (i.e., association with treatment response), we run a multiple equation regression as sensitivity analysis. Multiple equation regressions estimate coefficients and standard errors taking into account correlated errors in the included models. The results were similar to the single models which are, therefore, reported. In graphical illustrations of results, the procedure MARGINS was used to calculate predicted probabilities. All analyses were conducted with Stata 12.1 [51].

Results

Trauma history and baseline severity

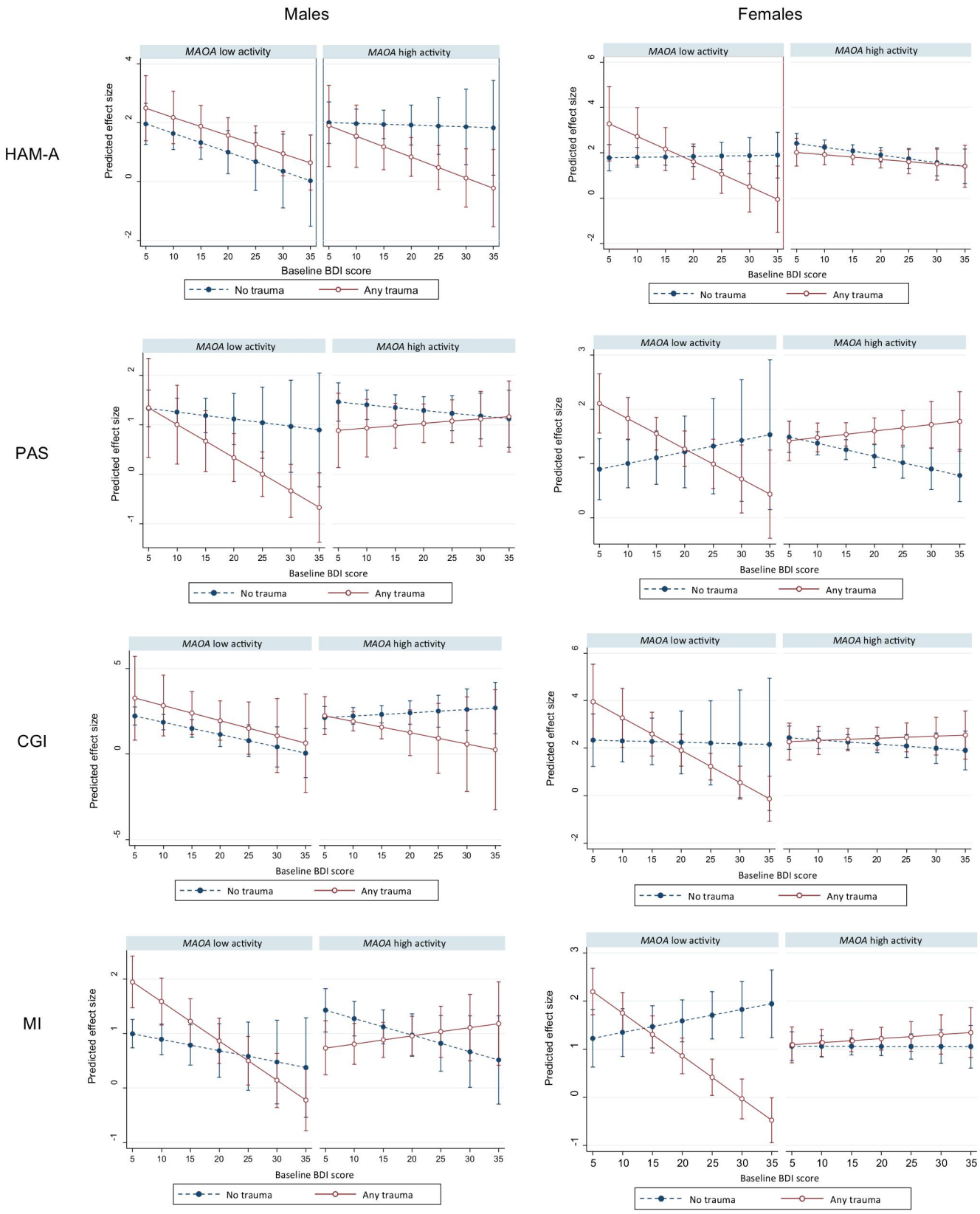
Among the patients with available genetic data, 30.0% of all male and 37.8% of all female patients reported at least one lifetime traumatic event. There were no differences in the probability of experiencing a traumatic event between low-active and high-active allele carriers. Among female patients, traumatized and non-traumatized individuals did neither differ in baseline severity of anxiety symptoms as assessed by HAM-A, PAS, CGI and MI nor in depression symptoms. The interaction between trauma history × *MAOA* genotype on baseline severity measures was not significant except that in individuals carrying the low-activity allele, the HAM-A score was higher in traumatized than non-traumatized individuals, resulting in a significant interaction [$b = 7.7$ (95% CI 1.0–14.3) $p = 0.024$]. Among female patients carrying the low-active allele baseline depression symptoms were also higher in traumatized than in non-traumatized patients [interaction: $b = 9.6$ (95% CI 1.7–17.6) $p = 0.018$] (Fig. 1).

Among male patients, we found no main effects of trauma history or interactions with *MAOA* genotype on baseline severity and baseline depression symptoms although the patterns of results go into the same direction as for females.

Table 1 Genotype, baseline variables and treatment effects by gender and trauma history

	No trauma		Any trauma	
	Males	Females	Males	Females
	$n = 42$	$n = 107$	$n = 18$	$n = 65$
Genotype, *n* (%)				
MAOA low activity	11 (26.2)	12 (11.2)	8 (44.4)	8 (12.3)
MAOA high activity	31 (73.8)	95 (88.8)	10 (55.6)	57 87.7)
Psychological assessment at BL, mean (SD)				
HAM-A	24.3 (4.9)	23.7 (4.9)	26.1 (7.0)	25.1 (5.8)
PAS	26.9 (10.7)	26.5 (9.5)	28.6 (8.1)	27.9 (10.4)
CGI	5.3 (0.8)	5.2 (0.7)	5.3 (0.6)	5.2 (0.8)
MI	2.6 (0.7)	3.0 (0.9)	3.0 (0.9)	3.1 (0.8)
BDI	15.2 (9.0)	15.9 (8.2)	16.0 (8.7)	17.7 (9.2)
Treatment effects sizes, mean (SD)				
HAM-A	1.8 (1.3)	2.0 (1.6)	1.4 (1.3)	1.7 (1.3)
PAS	1.3 (0.8)	1.2 (1.0)	0.8 (1.0)	1.5 (1.1)
CGI	2.1 (1.4)	2.2 (1.6)	1.8 (1.8)	2.3 (1.8)
MI	1.0 (0.8)	1.2 (0.9)	0.9 (0.6)	1.3 (0.9)

MAOA monoamine oxidase A, *BL* baseline, *HAM-A* Hamilton Anxiety Scale, *PAS* Panic and Agoraphobia Scale, *CGI* Clinical Global Impression Scale, *MI* Mobility Inventory, *BDI* Beck Depression Inventory


Males
Females
HAM-A
PAS
CGI
MI
MAOA low activity
MAOA high activity
Predicted effect size
Baseline BDI score
No trauma
Any trauma

◂**Fig. 3** Interaction trauma experience × *MAOA* gene × baseline depression symptoms predicting treatment outcomes by gender. *HAM-A* Hamilton Anxiety Scale, *PAS* Panic and Agoraphobia Scale, *CGI* Clinical Global Impression Scale, *MI* mobility inventory, *BDI* Beck Depression Inventory, *MAOA* monoamine oxidase A. *Error bars* indicate 95% confidence intervals. Models are adjusted for baseline values of the respective outcome and treatment condition of the original study design (accompanied vs not accompanied by the therapist). All three-way interactions among females are statistically significant ($p < 0.05$). Three-way interactions among males are only statistically significant for MI scores

Trauma history and fear reactivity

Among females, we did not find any differences between traumatized and non-traumatized individuals in self-reported anxiety or mean heart rate during exposure to a fearful situation before treatment. There were also no two-way interactions with the *MAOA* genotype. However, we found a three-way interaction trauma history × *MAOA* genotype × depression on both self-reported anxiety [$b = 0.4$ (95% CI 0.2–0.7) $p < 0.001$] and mean heart rate [$b = 0.8$ (95% CI 0.3–1.4) $p = 0.003$] during the exposure period indicating that in traumatized female patients carrying the low-activity allele, self-reported anxiety and mean heart rate decreased with increasing baseline depression symptoms at baseline (Fig. 2). Adjusting for the past 12-month PTSD diagnosis did not change these results. Among males, we did neither find differences between traumatized and non-traumatized individuals in self-reported anxiety or mean heart rate nor any two-way or three-way interactions with *MAOA*-genotype or baseline depression symptoms.

Trauma history and treatment outcome

Table 1 shows the treatment effects for traumatized and non-traumatized patients. Among females, we did not find any differences in treatment response between traumatized and non-traumatized individuals. We did also not find a two-way interaction trauma history × *MAOA* genotype on any of the examined outcome measures. However, there was a significant three-way interaction trauma history × *MAOA* genotype × depression symptoms on treatment outcome assessed by HAM-A [$b = 0.1$ (95% CI 0.01–0.2) $p = 0.027$], PAS [$b = 0.1$ (95% CI 0.04–0.2) $p = 0.004$], CGI [$b = 0.2$ (95% CI 0.01–0.3) $p = 0.037$] and MI [$b = 0.1$ (95% CI 0.1–0.2) $p < 0.001$] indicating that in traumatized female patients carrying the low-activity allele, effect sizes decreased with increasing baseline depression symptoms at baseline (Fig. 3).

Among males, we found a decreased treatment response in traumatized as compared to non-traumatized patients. However, this effect was limited to the PAS score [$b = -0.6$ (95% CI −1.1 to −0.1) $p = 0.012$]. Further, no significant two-way or three-way interactions with the *MAOA* genotype and baseline depression symptoms were found among males. Adjusting for the past 12-month PTSD diagnosis did not change the results patterns for females or males.

Discussion

In a post hoc analysis, we investigated the association between trauma history and treatment outcome in patients with panic disorder also considering the moderating role of the *MAOA* gene. In a sample of patients treated with manualized CBT, we found no effect of trauma history on treatment response in both female and male patients. This finding is in line with previous studies [52, 53], suggesting that CBT for panic disorder appears to be equally effective in traumatized and non-traumatized individuals. Like the majority of individuals exposed to traumatic events do not develop mental disorders [9, 10], psychological and neurobiological changes that could have an effect on response to CBT [15, 16] are also likely to occur only in a subgroup of those with traumatic experiences. This implies that CBT for panic disorder is generally effective in patients with a history of traumatic events and that research should focus on the identification of such subgroups.

In our study, we aimed at identifying such subgroups by taking into account the potential moderating role of the *MAOA* gene and depressive symptoms before treatment. There was no interaction between trauma history and *MAOA* gene on treatment response. However, a subgroup of traumatized females carrying the low-activity allele and reporting more depressive symptoms responded less to CBT treatment. This subgroup also showed emotional numbing during fear provocation prior to treatment. It has to be noted that these findings should be treated as preliminary since the number of individuals included in this subgroup was very small. Notwithstanding, if further supported in future investigations, these findings could have important theoretical and practical implications.

The relevance of the *MAOA* gene for the treatment outcome of CBT for panic disorder has already been demonstrated with the high-activity allele (also conveying risk for developing a panic disorder) being associated with poorer treatment outcomes [37]. Our preliminary findings suggest that the relative advantage of the low-activity allele in panic disorder patients might not apply for the subgroup of traumatized individuals. At this point, we can only speculate about possible mechanisms. Genetic variation in the *MAOA* gene might influence treatment outcomes for panic disorder via the availability of norepinephrine and serotonin [37] which are involved in extinction learning [54] and the regulation of fear conditioning and retrieval [55, 56]. Through a decreased availability of norepinephrine and serotonin in

high-activity allele carriers, these individuals might constitute a high-risk group for panic disorder and benefit less from CBT as previously observed [30, 37]. However, norepinephrine and serotonin seem to be related to fear mechanisms in a bimodal rather than in a linear manner with very low and very high levels being related to increased fear conditioning [55] and impaired extinction learning [57]. The experience of traumatic events is associated with a long-lasting increase in overall monoamine levels including both norepinephrine and serotonin [58]. In interaction with a genetically driven altered set-point towards higher monoamine levels (i.e., upon presence of the low-activity isoform), such additional trauma-related changes of neurotransmitter levels might raise serotonin and norepinephrine to a pathological range, while less negative effects are conveyed in *MAOA* high-activity allele carriers. This might give a conceivable explanation for the diminishing effect of traumatic events on the advantage of the *MAOA* low-activity allele in the context of CBT.

High levels of serotonin and norepinephrine are further related to aversive emotional states such as hyperarousal and anxiety [55, 59]. It is likely that some individuals exhibiting these states might (either intentionally or automatically) counteract these effects by a downregulation of intense emotional responses via emotional and behavioral avoidance or dissociation—both of which are frequently observed in traumatized individuals [60, 61]. Dissociation and experiential avoidance might prevent the re-evaluation of fear-related situations during CBT which has been shown to be a potential mechanism underling fear reduction [62]. In line, we observed the poorest treatment response in the avoidance behavior of these patients that seemed to be very stable. These assumptions are also supported by our finding that the subgroup with poor treatment outcomes was characterized by blunted fear reactivity when exposed to a fearful situation during the behavioral avoidance test. In accordance with this observation, reduced reactivity during the fear-provoking task has previously been associated with high levels of negative affect including depressive symptoms in patients with anxiety disorders [63, 64]. The fact that this subgroup of patients also reported more depressive symptoms at baseline is also highly conceivable since the frequent avoidance of emotional states is associated with the risk for depression symptoms [65, 66]. In summary, we hypothesize a theoretical model suggesting negative consequences of high levels of monoamines on cognitive processes and anxiety in traumatized low-activity *MAOA* allele carriers and an attempt to counteract these high levels with behavioral and emotional avoidance tendencies that diminish the effects of CBT. Although this model remains hypothetical so far, it fits well with both our findings and previous observations. Moreover, it provides a useful framework for future investigations on the association between traumatic events and treatment outcomes including its genetic and non-genetic moderators. Importantly, it also provides several potential targets to adapt and improve existing interventions.

This study has some important limitations. First, as stated above, the careful consideration of a three-way interaction led to very small analysis groups. Thus, the respective findings have to be interpreted with caution and should be seen as exploratory. Second, this study is based on post hoc analyses of a randomized clinical trial. Thus, patients were not randomized based on the independent variables. Third, comorbid disorders other than PTSD were not considered in the present analyses but might have affected treatment outcomes. Fourth, patients were treated within academic centers according to a manual-based CBT and any generalization to less controlled natural therapy settings has to be done with caution. Finally, the existing literature suggests that the associations found in this study are more likely to be attributable to early traumatization than to traumatization in general which should be explored in greater detail in future investigations.

Taking these limitations into account, we provide evidence that CBT for panic disorder is equally effective in traumatized and non-traumatized individuals. There is first evidence that a subgroup of traumatized individuals carrying the low-active variant of the *MAOA* gene might not as much benefit from exposure-based CBT for panic disorder. These patients also report more symptoms of depression and show emotional numbing during fear provocation prior to treatment. These findings warrant further investigation specifically designed to investigate the interaction between trauma exposure, *MAOA* gene and depressive mood as well as potential mechanisms. Such investigations might reveal further insights into treatment-resistant subtypes of anxiety disorders and allow considering more strongly individual characteristics of heterogonous patients currently grouped in distinct diagnostic categories exclusively based on subjective symptom reports. This might result in the adaptation of interventions to increase the number of patients that can be effectively treated.

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Compliance with ethical standards

Ethical standards All participants provided informed consent. The study protocol was approved by the Ethics Committee of the Medical Faculty of the Technische Universität Dresden (EK164082006).

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9 Discussion and future directions

The aims of this thesis were to (1) provide estimates on the prevelance of traumatic event exposure and trauma-related mental disorders in the general population and high-risk populations and (2) investigate moderators of adverse mental health consequences following traumatic event exposure.

9.1 Prevelance of traumatic event exposure and trauma-related mental disorders

The main findings of chapters 2 and 3 can be summarized as follows:

- The majority of individuals is exposed to at least one traumatic event in their lives
- Only a small minority of trauma-exposed individuals develops mental disorders
- This also apllies to populations with a high risk for multiple and/or severe trauma exposure

These findings underline that the vast majorty of individuals exposed to a traumatic event is not in need for early interventions because they would not develop any adverse mental health consequences. This seems to be the case for any random traumatic event in the general population (e.g. conditional PTSD prevalence approx. 4%), but also for more severe events (e.g. war exposure) where the conditional prevalence might be higher but usually still markedly below 50%. We also showed that soldiers deployed to military missions (as an assumed high-risk population) do not have a higher risk for mental disorders compared to the general population; and that this risk is only somewhat elevated in case of high combat exposure. These observations are in line with many previous findings from epidemiological studies in the general population (Breslau, 2009) and high-risk populations such as soldiers (Macmanus et al., 2014), firefighters (Harvey et al., 2016), refugees (Turrini et al., 2017), policemen and medial services (Donnelly, 2012). This has important implications for the application of early interventions in trauma-exposed individuals. As already described in the first chapter, the majority of these interventions

have a limited efficacy. Considering that only a small minority of trauma-exposed individuals develops mental health problems, this limited efficacy is not surprising. Trauma exposure alone seems to be a poor indicator of need for interventions. This becomes even more evident when considering that even populations with higher exposure to traumatic events do not necessarily have higher rates of mental disorders (see chapter 3) which clearly suggests that risk of psychopathology is moderated by other variables. Thus, a deep understanding of these moderators is essential to be able to improve early preventive efforts after trauma exposure. This notion becomes even more important when considering that interventions in individuals that are not in need for interventions is not only ineffective but can also have serious adverse effects (Sijbrandij, Olff, Reitsma, Carlier, & Gersons, 2006).

9.2 Moderators of adverse mental health consequences following traumatic events

The main findings of chapters 4 to 8 can be summarized as follows:

- Individuals with a higher susceptibility to negative emotions of others show a higher stress reactivity after trauma exposure
- Males with childhood traumas show a higher increase in alcohol craving after trauma exposure
- Individuals with lower basal cortisol levels have a higher risk of increased PTSD symptoms and alcohol use following trauma exposure
- A subgroup of traumatized female panic disorder patients with the low-active variant of the *MAOA* gene shows an altered fear reactivity and benefits less from exposure-based psychotherapy

These findings are a significant contribution to the field of trauma-related mental health research since they suggest novel targets for moderating factors (e.g. the susceptibility to negative emotions of others) and show the relevance of previously discovered moderators in a novel

context (e.g. childhood traumas and trauma-related alcohol craving). They also contribute to an advanced understanding of the processing of traumatic events. In particular, they futher confirm that multiple, multi-modal variables are involved including genetic and biological, environmental and personality factors. While the exact role and practical value of some of the identified moderators (e.g. emotional contagion, *MAOA* gene) have still to be determined, others already represent promising targets for risk markers before or in the direct aftermath of traumatic event exposure. For example, basal cortisol levels are relatively easy to sample and analyze (Stalder & Kirschbaum, 2012) and could be used within a larger risk assessment framework together with other variabels (e.g. mental health, childhood adversities) in high-risk populations such as military personnel. A first attempt of such a risk assessment to identify individuals at need for selective interventions already showed promising results (Kessler et al., 2014). Although the presented findings on moderators are encouraging, they can only be small puzzle pieces in a larger future agenda towards a better risk prediction as a basis for effective early interventions following trauma exposure.

9.3 Future directions

Multimodal assessments and research networks

The findings presented in this thesis clearly show that multi-modal measurements are needed to capture relevant moderators of trauma-related mental health consequences. This requires a conceptualization of moderating factors of different levels, e.g. as suggest by the Research Domain Criteria (RDoC) framework (Cuthbert, 2014). Such a multi-modal approach requires diverse study designs (epidemiological, experimental, interventional) and methodological expertise to be able to rigorously assess, analyze and integrate multi-modal measures. Moreover, many variabels are likely to interact and associations might differ between populations, trauma types and outcomes. Thus, large, heterogeneous samples and study programs are needed. Since

such study programs are very costly and challenging, it is neseccery to build and establish research networks for trauma research as it has been done for several othe research areas (Haro et al., 2014; Kessler & Ustün, 2004).

Understanding core processes

The number of factors identified as potential moderators of trauma-related consequences is constantly growing. Although the identification such moderators (as in this thesis) is valuable, it is sheer imposible to assess all this variables in clinical practice. In fact, it is even unnecessary since many variables overlap or are correlates of an underlying mechanism. For example, alterations in cortisol levels have been assocated with both genetic polymorphisms and exposure to childhood traumas (Schalinski et al., 2015; Tucker-Drob et al., 2017). As a result, many moderators show only modest associations with the outcome of interest. Thus, a main challenge is to integrate the findings on moderators at different assessment levels and to identify the core underlying variables and processes, for example by applying network and machine learning models to large multi-modal datasets (Hammamieh et al., 2017).

Translating research into routine assessments

Even if the large number of potential moderators of adverse trauma-related consequences can be reduced to several core elements, the assessment of these variabels would still have to be adapted to the requirements of routine care. The largest need for selective preventive measures is in intensive care units, routine assessments in high-risk occupations (e.g. soldiers, police officers) or (for decisions about treatment response after trauma exposure) in- and out-patient health care facilities. These settings are mostly characterized by limited time and ressources to assess potentially relevant factors. Thus, the assessment of moderators of trauma-related consequences has to be time-efficient and easy to utilize.

Translating research into targeted interventions

Although knowledge on moderators of adverse trauma-related consequences can be useful to identify individuals who might benefit from existing interventions, it should also be used to develop novel tailored interventions. This requires moderators that have a causal effect and can be modified or prevented. However, the causal nature of associations is unclear for many factors that have been suggested as potential moderators so far. One reason is that most variables cannot be experimentally manipulated in a randomized trial. Thus, future research should incorporate methods that are able to estimate causal effects from observational data, such as propensity score methods (Schafer & Kang, 2008), standardization and inverse probability weighting (Hernán & Robins, 2006) or directed acyclic graphs (VanderWeele & Robins, 2010).

In summary, the identification, integration and translation of factors moderating adverse outcomes after traumatic event exposure has a high potential to improve the selection of vulnerable individuals and substantially increase both efficacy and effectiveness of early interventions.

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Appendix

Erklärung zu Eigenanteilen an den Publikationen

Trautmann, S. & Wittchen, H.-U. (2018). Post-Traumatic Stress Disorder in Europe. In: Nemeroff, C. & Marmar, C. (eds.). *Post-Traumatic Stress Disorder*. New York: Oxford University Press.

Eigenanteil: Konzeption, Literaturrecherche, Verfassen des Manuskriptes

Trautmann, S., Goodwin, L., Höfler, M., Jacobi, F., Strehle, J., Zimmermann, P., & Wittchen, H.-U. (2016). Prevalence and severity of mental disorders in military personnel: a standardised comparison with civilians. *Epidemiology and Psychiatric Sciences*, 1–10.

Eigenanteil: Konzeption, Beteiligung an der Datenerhebung, Analyse und Interpretation der Daten, Literaturrecherche, Verfassen des Manuskriptes

Trautmann, S., Muehlhan, M., Kirschbaum, C., Wittchen, H.-U., Höfler, M., Stalder, T. Steudte-Schmiedgen, S. (2017). Biological stress indicators as risk markers for increased alcohol use following traumatic experiences. *Addiction Biology*.

Eigenanteil: Konzeption, Beteiligung an der Datenerhebung, Analyse und Interpretation der Daten, Literaturrecherche, Verfassen des Manuskriptes

Steudte-Schmiedgen, S., Stalder, T., Schönfeld, S., Wittchen, H.-U., **Trautmann, S.**, Alexander, N., Miller, R., Kirschbaum, C. (2015). Hair cortisol concentrations and cortisol stress reactivity predict PTSD symptom increase after trauma exposure during military deployment. *Psychoneuroendocrinology,* 59, 123-133.

Eigenanteil: Beteiligung an der Datenerhebung, Unterstützung bei der klinischen Interpretation der Daten, Kritische Durchsicht und Anmerkungen beim Verfassen des Manuskriptes

Trautmann, S., Reineboth, M., Trikojat, K., Richter, J., Hagenaars, M., Kanske, P., Schäfer, J. (2018). Susceptibility to others' emotions moderates immediate self-reported and biological stress responses to witnessing trauma exposure. *Behavior Research and Therapy*.

Eigenanteil: Konzeption, Einwerbung und Durchführung der Studie, Analyse und Interpretation der Daten, Literaturrecherche, Verfassen des Manuskriptes

Trautmann, S., Kräplin, A., Dietrich, R., Richter, J., Muehlhan, M. (2018). Stress-induced alcohol craving after psychological trauma: the role of childhood trauma and stress reactivity. *Psychopharmacology*.

Eigenanteil: Konzeption, Einwerbung und Durchführung der Studie, Analyse und Interpretation der Daten, Literaturrecherche, Verfassen des Manuskriptes

Trautmann, S., Richter, J., Muehlhan, M., Hoefler, M., Wittchen, H.-U., Domschke, K., Stroehle, A., Hamm, A., Weber, H., Kircher, T., Arolt, V., Gerlach, A., Alpers, G. , Fydrich, T., Lang, T., Reif, A. (2017). Does prior traumatization affect the treatment outcome of CBT for panic disorder? The potential role of the *MAOA* gene and depression symptoms. *European Archives of Psychiatry and Clinical Neurocience*.

Eigenanteil: Konzeption, Analyse und Interpretation der Daten, Literaturrecherche, Verfassen des Manuskriptes

Eigenständigkeitserklärung

Hiermit versichere ich, Sebastian Trautmann, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Die aus fremden Quellen direkt oder indirekt übernommenen Gedanken sind als solche kenntlich gemacht. Die Arbeit wurde bisher weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

Die Habilitationsschrift wurde von Juli 2015 bis August 2018 am Institut für Klinische Psychologie und Psychotherapie der Technischen Universität Dresden unter der Betreuung von Prof. Dr. Hans-Ulrich Wittchen angefertigt.

Die Habilitationsordnung erkenne ich an.

Dresden, den 28.09.2018

Sebastian Trautmann